1-A-1 The Role of Gut Bacteria in Obesity Predisposition in Preterms

Elisha Phull[1], Diana Bedoya[1]

[1]Simon Fraser University

Objective: Preterm birth predisposes infants to childhood and adult obesity. Shifts in healthy gut bacteria populations are also evidenced in the preterm state due to the etiology of preterm birth. Previous research shows gut bacteria involved in the endocrine system, indicating that gut bacteria have systemic effects, a role beyond local physiology in the digestive system. Additionally, certain bacterial populations can affect energy harvesting, and, accordingly, energy balance. In this review paper, we propose a possible mechanism by which the preterm gut bacteria directly influences feeding circuit to predispose a preterm child to obesogenic feeding behaviour. Method: Keywords were entered into Google Scholar, PubMED, Mendeley as phrases. Article inclusion criteria includes review and primary research displayed on the first page of relevance and published after 2000. Papers were accepted if abstracts described preterm infant obesity, gut bacteria, neurocognition, development, emotional behaviour, energy harvesting, energy regulation, enteric nervous system, food intake behaviour. Results: Gut bacteria act as afferent stimulates of the vagal nerve, which contribute to the differential synaptogenesis of POMC and ARg neurons within the hypothalamus during the critical growth period during preterm infant development. Conclusion: Further research into gut-brain development and mechanism of feeding behaviour may provide evidence-based support to use gut bacteria as a preventative treatment to reduce incidence of obesity in the preterm infants.

1-A-2 The role of Clusterin and its putative Plexina4 receptor in the developing zebrafish brain

Zachary Nurcombe[1], Carrie Hehr[1], Sarah McFarlane[1]

[1]University of Calgary

Two proteins have been found to be associated with Alzheimer's disease; Plexina4, a transmembrane protein involved in development and axon guidance of the central nervous system (CNS), and; Clusterin, a secreted heat-shock protein with many biological roles, including as a regulator of apoptosis. In Alzheimer's disease, Plexina4 is downregulated, while Clusterin exhibits increased expression. A recent study showed that Plexina4 is a receptor for Clusterin in the adult nervous system, and that this interaction may promote neuronal survival. This study uses zebrafish embryos to determine if Clusterin and Plexina4 interact to promote neuronal

survival in the developing CNS. We found by using RNA in situ hybridization that clusterin is expressed in the floorplate of the hindbrain by 36 hours post-fertilization, with plexina4 expressed in bilateral cell clusters on either side of this expression domain. These data support the idea that Clusterin acts as a ligand for Plexina4 in the embryonic zebrafish hindbrain. In zebrafish, we are manipulating Clusterin and/or PlexinA4 function by injections of antisense morpholino oligonucleotides to mediate protein knock-down or mRNA for gain-of-function, as well as with genetic loss of plexina4. We are assaying neuronal survival in brain development, with a particular focus on ventral hindbrain. If the interaction between Clusterin and Plexina4 promotes neuronal survival in the developmental context, the results could shed light on the role of Clusterin and Plexina4 in Alzheimer's disease.

1-A-3 Uncovering the molecular pathways regulating dopaminergic neurons axon guidance through PlexinC1

Caroline Lafrechoux[1], Martin Lévesque[1]

[1]Université Laval

Midbrain dopaminergic neurons regulate a wide range of functions, from locomotion to behaviour. They can be distinguished in two subtypes located in the Ventral Tegmantal Area (VTA) and the Substancia Nigra compacta (SNc). During development those midbrain dopaminergic neurons project to the cortex, striatum and lymbic areas to form respectively the mesocortical, nigrostial and mesolymbic pathways. Mechanisms regulating their guidance throughout development remain largely unknown. Here, we show that midbrain dopaminergic guidance to the cortex and striatum is mediated through the chemorepulsive action of the Semaphorin 7a (Sema7a) and its membrane receptor, PlexinC1. When binding to the receptor, Sema7a induces a signaling cascade leading to the cytoskeletal modulation of the growth cone. In order to identify the molecular effectors of such changes, primary culture and explants of midbrain dopaminergic neurons expressing PlexinC1 were cultivated in vitro. After stimulation with Sema7a, dopaminergic neurons show an increased level of activation of Src family kinases (SFK). To further confirm the importance of SFK in axon guidance, their activity was chemically and genetically blocked in vitro and in vivo. Altogether our results indicate that SFK acts downstream of Sema7a/PlexinC1 interaction to guide dopaminergic axons.

1-A-4 Identification of novel Schwann cell-derived factors regulating axonal growth through cell-cell communication modelling

Jeremy Toma[1], Scott Yuzwa[1], David Kaplan[1], Freda Miller[2]

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

Mixed peripheral nerves contain axons from multiple neuron types including motor, sensory and sympathetic neurons. During nerve development and regeneration, Schwann cells secrete factors that are critical for normal growth and guidance of these different axon types. While several growth factors necessary for support of individual axon types are known, important questions remain: What is the full complement of Schwann cell-derived factors required to execute a complete developmental and reparative program in peripheral axons? Are these factors unique to axon type or do Schwann cells secrete a generalized set of factors targeting multiple axon types? We have taken a computational systems biology approach to address these questions. Using proteomic and/or transcriptomic data derived from Schwann cells and sensory, motor, and sympathetic neurons, we generated communication models to predict ligand-receptor interactions between Schwann cells and peripheral neurons respectively. Through this approach, several predicted (including novel) Schwann cell-neuron interactions were found to be conserved across neuron type and present in both the developing and injured nerve. Novel predicted factors including BMP-7 and VEGF-C were found to regulate the growth of sensory neurons ex vivo, providing evidence to validate the interaction models. Our results suggest that Schwann cells secrete a large number of factors that have roles in supporting, growing, guiding and regenerating diverse peripheral axon types during nerve development and following injury.

1-A-5 Developmental emergence of adult neural stem cells as revealed by single cell transcriptional profiling

Scott Yuzwa[1], Michael Borrett[1], Brendan Innes[2], Anastassia Voronova[1], Troy Ketela[3], David Kaplan[1], Gary Bader[2], Freda Miller[2]

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

Adult neural stem cells (NSCs), responsible for olfactory learning and aspects of brain repair, derive from embryonic precursors, but little is known about how or when this occurs. We have addressed this issue using single cell RNA sequencing at multiple developmental timepoints to

analyze the embryonic murine cortex, one source of adult forebrain NSCs. We computationally identify all major cortical cell types, including the embryonic radial precursors (RPs) that generate adult NSCs. We define the initial emergence of RPs from neuroepithelial stem cells at E11.5. We show that by E13.5 RPs express a core transcriptional identity that is maintained and reinforced throughout their transition to a non-proliferative state between E15.5 and E17.5. These slowly-proliferating late embryonic RPs share a core transcriptional signature with quiescent adult forebrain NSCs (qNSCs) that persist and are mobilized to produce neurons throughout life. Thus, our findings establishing a transcriptional core identity of RPs/qNSCs enable us to investigate whether genetic alterations as occur in maternal insults and neurodevelopmental disorders perturb adult qNSC biology, determine how the environment alters qNSC function, and ask how qNSCs persist and are mobilized throughout life for learning and repair. With regard to the latter question, we describe here the potential identification of regulators of embryonic and adult RP/qNSC quiescence that mediate the transition from embryonic cortical RPs to qNSCs.

1-A-6 A population of dormant, ventricle-contacting neurogenic precursors in the adult forebrain

Sandra Joppé[1], Loic Cochard[1], Pierre Ameslon[1], Laura Hamilton[1], Louis-Charles Levros[1], Anne Aumont[1], Karl Fernandes[1]

[1]Université de Montréal

The subventricular zone (SVZ) is the major neurogenic niche in the adult mouse brain and produces thousands of neurons per day. This production is possible due to adult neural stem cells (NSCs), which are maintained is this region throughout life. It is currently accepted that SVZ NSCs are a heterogeneous population that differ in their individual properties, such as cell cycle status or progeny production, however, approaches for studying specific NSC subpopulations are limited. We used a combination of adult brain electroporation and transgenic models to test the hypothesis that ventricle-contacting GFAP-expressing cells are a population of quiescent NSCs (qNSCs) that are upstream of the more actively dividing NSCs (aNSCs). In vivo lineage tracing confirmed the presence of a highly quiescent ventricle-contacting GFAP+ precursor that produces olfactory interneurons. Intriguingly, however, this precursor generates only weak neuroblast/neuron production, does not contribute appreciably to the aNSC pool, and is not recruited during SVZ regeneration after Ara-C treatment. These data indicate that, although electroporated ventricle-contacting GFAP+ cells have the capacity to produce neuronal progeny,

this may not be their primary function under physiological or regenerative conditions. Thus, at least some ventricle-contacting GFAP+ cells are neurogenic precursors that are not upstream of the aNSC pool, an observation not predicted by the current model of the SVZ niche.

1-A-7 Dormant neural stem cells in the adult brain are activated upon ectopic stimulation of EGFR signalling

Loic Cochard[1], Sandra Joppé[1], Anne Aumont[1], Karl Fernandes[1]

[1]Université de Montréal

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, our objectives are to: i) dissect the roles of major EGFR-induced signaling pathways in neural stem/progenitor functions in vitro (survival, proliferation, differentiation), and ii) determine whether qNSCs can be activated in the adult brain by modulating these pathways in vivo. Using the colony-forming neurosphere method, we first isolated and expanded forebrain NSCs and used these stem/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 stem/progenitor proliferation required activation of all three of these pathways, we are now using an adult brain electroporation procedure to overexpress constitutively active EGFR in qNSCs in vivo. These studies will provide insights into potential strategies for recruiting dormant NSCs to promote brain repair. This work supported by CIHR.

1-A-8 Pannexin1 regulates neurite development via a novel protein-protein interaction with Collapsin response mediator protein 2

Xiaoxue Xu[1], Leigh Wicki-Stordeur[2], Mei Liu[1], Maria Weaver[1], Catherine Choi[1], Leigh Anne Swayne[1]

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

Neurite development requires precise remodelling of cytoskeletal proteins, namely tubulin and actin. As an ATP-release channel-forming protein, Pannexin1 (Panx1) is reportedly involved in synaptic plasticity. Our lab has previously shown that Panx1 negatively regulates neurite outgrowth. Here we further observe that blocking Panx1 with probenecid favors microtubule stabilization. Providing potential insight into the underlying mechanism(s), our unbiased proteomic analysis revealed a novel interaction with a microtubule-associated protein-collapsin response mediator protein 2 (Crmp2). Immunoprecipitation and Proximity ligation assay confirmed the interaction, in vivo and in vitro. In vitro binding assays between purified proteins suggested Panx1 was able to interact with Crmp2 directly via its C-terminus. Therefore, we hypothesized that Panx1 regulates neurite development via this novel interplay. We next discovered that pharmacological inhibition of Panx1 markedly reduced the Panx1/Crmp2 interaction and re-localized Crmp2 to the distal tips of neurites, where microtubules are relatively more dynamic. Intriguingly, the Panx1 blocker also decreased Crmp2 phosphorylation at serine 522, increasing the proportion of the "active" form of Crmp2. In summary, these results reveal crosstalk between Panx1 and Crmp2, in which Panx1 effectively "keeps the brakes" on neurite outgrowth by physically sequestering Crmp2. Loss of Panx1 function during development might remove this "brake", thereby releasing more active Crmp2 to stabilize new neurites.

1-A-9 Development of Spine Interactions in Auditory Cortex

Megan Boucher-Routhier[1], Jean-Philippe Thivierge[1]

[1]University of Ottawa

It has been suggested that changes in dendritic spine configurations form the physical correlates of long-term memory (LTM). The locations of dendritic spines are reorganized following experience-dependent plasticity. A key phenomenon that occurs with dendritic spines is the formation of both functional clusters that share correlated neural activity, and anatomical clusters of spines that are located within close proximity. We analyzed data from two-photon imaging of dendritic spines in the auditory cortex of mice to determine if changes in spine morphology over time (i.e., volume and shape of the spines) were correlated with spatial distance along dendritic segments. Previous literature has examined how the morphological features of spines (e.g., shape, volume) influence their likelihood of survival; here, we have expanded on previous work to investigate whether spines in clusters share more similar changes

than those farther apart. We found that there is a significant correlation between measures of both shape and volume of dendritic spines, and the Euclidean distance between pairs of spines. Furthermore, pairs of spines that were located close together in physical space showed correlated changes in both volume and shape. This work highlights the importance of understanding how spines are related within spatial distance in order to determine how dendritic plasticity, and synaptic clustering occurs over the course of development.

1-A-10 Differential contributions of NMDA receptor subtypes to juvenile lamina II synaptic responses

Hadir Mahmoud[1], Michael Hildebrand[1]

[1]Carleton University

The heteromeric N-Methyl-D-Aspartate receptor (NMDAR) is a crucial regulator of excitatory synaptic transmission throughout the CNS. Specific subtypes of the GluN2 subunit (GluN2A - 2D) differentially contribute to the kinetic properties and physiological roles of NMDARs. Previously, we have demonstrated a dominance of slow GluN2B- and GluN2D-containing NMDARs at lamina I adult spinal synapses, unlike the fast GluN2A-dominated synapses found throughout most of the mature CNS. However, the functional contribution of specific GluN2 subunits is not well characterized for lamina II neurons, which are critical for spinal pain signaling and modulation. To identify the functional contribution of GluN2A and GluN2B subunits to NMDAR responses at juvenile (P6-P21) lamina II synapses, we performed whole-cell patch clamp recordings of miniature excitatory postsynaptic currents (mEPSCs) in the presence and absence of subtype-specific pharmacological blockers. We observed a relatively equal contribution of GluN2A and GluN2B at juvenile lamina II synapses. Moreover, a shift in the contribution of GluN2-mediated NMDAR responses was observed postnatally, with GluN2A being more prominent in younger (P6-P10) and GluN2B in older (P11-16) animals. We also identified a slower GluN2D-like NMDAR component that is resistant to both GluN2A- and GluN2B-specific blockers and increases in prominence during postnatal development. These findings will provide key insights into the role of specific NMDAR subtypes in nociceptive signaling at juvenile spinal synapses.

1-A-11 Methylglyoxal suppresses the translation of Notch1 mRNA to alter neural stem cell homeostasis in the developing mouse cortex

Deivid Rodrigues[1], Holly Liu[2], Fatin Ishraque[2], Jose Perez[2], James Ellis[1], David Kaplan[1], Guang Yang[2]

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

Methylglyoxal is a toxic metabolite that arises during glycolysis. Genetic and environmental perturbations that cause an abnormal increase of methylglyoxal have been implicated in neurodevelopmental disorders, such as autism spectrum disorder and schizophrenia. Using the mouse cerebral cortex as a model system, we recently found that aberrant increase of methylglyoxal in neural stem/precursor cells (NPCs) causes NPC depletion and premature neurogenesis in the developing brain, leading to long-term changes postnatally in neuroanatomy and in behaviors relevant to autism spectrum disorder. However, the molecular mechanisms that mediate the adverse effects of methylglyoxal on NPC homeostasis has not been explored. Here, we show that methylglyoxal reduces Notch1 protein levels in both mouse cortical NPCs and human ESC-derived NPCs. The reduction of Notch1 protein abundance is at the translational level and mediated by the binding of the glycolysis enzyme GAPDH to an AU-rich element within the 3`UTR of Notch1 mRNA. Methylglyoxal post-translationally modifies GAPDH, which inhibits the enzymatic function of GAPDH in the glycolytic pathway and engages it as a RNA-binding protein to suppress Notch1 mRNA translation. Consistently, decreasing GAPDH levels or restoring Notch signaling in NPCs rescues methylglyoxal-induced NPC depletion and premature neurogenesis in the developing mouse cortex. Thus, our data suggest that methylglyoxal alters NPC homeostasis by GAPDH-mediated repression of Notch1 mRNA translation.

1-A-12 Semaphorin3fa Mediates Retinal Progenitor Cell Dynamics and Differentiation

Rami Halabi[1], Carrie Hehr[1], Sarah McFarlane[1]

[1]University of Calgary

The developing eye requires the concerted and coordinated efforts of multiple intrinsic and extrinsic factors. During retinal neurogenesis, progenitor cells expand in population and undergo waves of sequential differentiation with spatio-temporal constraints to generate the correct numbers and proportions of the seven cell types of a functional retina. We aimed to further understand this complex gene regulatory network which determines where and when

progenitor cells divide and terminally differentiate. Here we describe a novel role for the secreted chemorepellent molecule, Semaphorin 3f (Sema3f), as an extrinsic regulator of this process. Through CRSIPR/Cas9 mediated mutagenesis, we analyze global loss of sema3fa on retinal neurogenesis using zebrafish (Danio rerio). While mutants display no gross morphological defects, retinal progenitor cell cycle stage and differentiation programs, are impaired. Specifically, sema3fa mutants present with reduced progenitor cell proliferation and loss of progenitor maintenance markers such as Notch pathway ligand, DeltaA, and G1 cell cycle marker, CyclinD1. Further, early neurogenesis programs are disrupted suggesting a failure of progenitor cell competency to other extrinsic cues to initiate neural differentiation. Ultimately this results in poorly differentiated and laminated eyes. These data highlight the importance of Sema3fa in governing the regulatory network from progenitor to differentiating neuron in the retina.

1-A-13 The effects of perinatal high fat diet on myelination, microglia, and behavioral deficits associated with neurodevelopmental disorders in the offspring

Maude Bordeleau[1], Giamal Luheshi[1], Marie-Eve Tremblay[2]

[1]McGill University, Doulas Mental Health Institute, [2]Centre de recherche du CHU de Québec

Myelination can be disrupted on exposure to environmental stressors, including maternal diet, which can lead in some cases, to the development of brain disorders in the offspring. Recent studies in mice revealed that perinatal high fat diet (pHFD) induces, in the offspring, hypomyelination and neuroinflammation, associated with behavioral deficits relevant to developmental disorders. We hypothesize that these changes may be linked to the disruption of microglial function leading to abnormal myelination and behavioral deficits. To investigate this, female mice were fed with control or pHFD for 4 weeks before mating, during gestation, and until weaning of the litter. Phenotypic characteriation of the offspring was performed using open field, 3-chambers assay, marble burying assay, elevated-plus maze and prepulse inhibition at adolescence and adulthood. Blood and brain of the offspring were collected after behavioral assessment at postnatal day (P)30 to evaluate myelination and microglial function using rt-qPCR and immunohistochemistry. Another cohort was sacrificed at P30 to assess ultrastructural changes of microglial interactions with myelinated axons and synapses by electron microscopy. Our results reveal that pHFD alters inflammation and leads to the development of sensorimotor deficits and stereotypic behaviors. Gene expression and ultrastructural analyses are being conducted to understand the relation between inflammation and behavioral deficits. Our study

will provide new insights into the impact of pHFD exposure on microglial function and their role in myelination.

1-A-14 Impact of energy consumption and autophagy on neuronal migration

Cedric Bressan[1], Marina Snapyan[1], Dave Gagnon[1], Simon Labrecque[1], Johannes Klaus[2], Martin Parent[3], Paul De Koninck[1], Stephen Robertson[4], Silvia Cappello[2], Armen Saghatelyan[5]

[1]CERVO Brain Research Center, [2]Max Planck Institute of Psychiatry, [3]Université Laval, [4]Dunedin School of Medicine, University of Otago, [5]CERVO Brain research center, Laval University

Cell migration is ATP dependent process with dynamic morphological remodeling leading to the formation of protein aggregates and organelle damage. Here we evaluated the involvement of autophagy, a catabolic pathway that maintains cellular homeostasis, and its link to energy level in neuronal migration. We used mouse rostral migratory stream as a model system and optically monitored energy consumption in neuroblasts using a ratiometric ATP/ADP sensor. The ATP/ADP ratio dropped during migratory phases and recovered to its baseline level during stationary periods. Time-lapse monitoring of autophagic flux also showed an active autophagic flux with increased density of autophagosomes during stationary phases of migrating neuroblasts. Blocking AMPK, an energy level sensor and autophagy activator, or genetic impairment of autophagy in neuroblasts led to decrease in cell migration. By contrast, AMPK blockade in autophagy-deficient neuroblasts had no effect on cell migration suggesting the involvement of energy levels in autophagy activation. We next asked if autophagy is altered in disorders associated with neuronal migration defects. Mutations in genes encoding for cadherin ligand (DCHS1) and receptor (FAT4) leads to periventricular heterotopias in humans. We observed an impairment of autopahgy in human organoids with mutated FAT4 and DCHS1 genes as well as alterations in the migration of progenitor cells with these mutations. Altogether, we show that autophagy may be activated because of energetic needs and is required for cell migration under normal and pathological conditions.

1-A-15 Loss of microglia compromises survival and sensorimotor reflexes of mouse pups after perinatal insults

Sophie Tremblay[1], Alex Pai[1], Weiwei Meng[1], Daniel Goldowitz[2]

[1]Centre for Molecular Medicine and Therapeutics, [2]University of British Columbia

Background: Extreme preterm infants are exposed to multiple stressors including perinatal cerebellar haemorrhage (CBH) and postnatal infection, two major risk factors for neurodevelopmental impairments. Given microglia involvement in inflammatory functions across the central nervous system, they may play a central role in the pathogenesis of cerebellar injury in developing brains. By using a transgenic mouse model, the role of microglial cells on short-term outcomes in CBH and early inflammation (EIS) will be studied. Methods: Conditional transgenic mice dependent on diphtheria toxin (DT) intracerebellar injection to deplete CX3CR1-positive cells were made and CBH was induced by a local injection of bacterial collagenase at P2 combined with an intraperitoneal LPS injection to mimic EIS. Results: Survival is mainly affected by being exposed to DT (50%) or to CBH (48,6% to 54,6%) compared to control (71,4%) or vehicle-exposed mice (62,6%). CX3CR1-depleted mouse pups exposed to combined insults have smaller corrected brain weight compared to CX3CR1-depleted mice exposed to single insult (*$P<0.05$). Functional assessment reveals a significant delay of grasping acquisition in CX3CR1-depleted pups exposed to EIS compared to non-depleted mice (*$P=0.03$) or CX3CR1-depleted pups exposed to vehicle (**$P<0.0053$). Conclusions: Microglia-depleted mice exposed to early inflammation have worse neonatal outcomes including compromise survival and a delay in grasping acquisition compared to non-depleted mice, suggesting a potential protective role of microglial cells after EIS insult.

1-A-16 Regulation of mossy fiber-granule cell synaptic plasticity by a novel FMRP-Cav3.1 calcium channel association

Xiaoqin Zhan[1], Giriraj Sahu[1], Hadhimulya Asmara[1], Charmaine Szalay[1], Gerald Zamponi[1], Raymond Turner[1]

[1]University of Calgary

Our recent work found that the long-term potentiation of mossy fiber input to granule cells involves a dramatic increase in postsynaptic excitability, which is also strongly regulated by an ion channel complex consisting of Cav3 (T-type) calcium and Kv4 (A-type) potassium channels (Cav3-Kv4). This study examined how regulation of Cav3 and Kv4 channels could contribute to disorders of synaptic plasticity in the Fragile X Syndrome (FXS). We found that FMRP coimmunoprecipitates (coIPs) with Cav3.1 and forms an association close enough to support Foerster Resonance Energy Transfer (FRET) expressed in tsA-201 cells. Infusion of a short N-terminal fragment of FMRP (FMRP(1-298)) through a recording electrode left-shifted the Vh of

Cav3.1 channels expressed in tsA-201 cells and Kv4 Vh in granule cells. Mossy fiber LTP and the associated left-shift in Kv4 Vh is absent in FMRP-/- mice but rescued by infusing FMRP(1-298) through the patch recording electrode in vitro. A left shift in the Cav3 Vh expressed in tsA-201 cells, or of Cav3-Kv4 Vh in granule cells was induced by bath applying a tat-FMRP(298) construct to facilitate access across cell membranes. Preliminary data of tail vein injections of tat-FMRP(298) showed decreased hyperactivity in FMRP-/- mice in behavioral tests. Our findings are the first to show an association between FMRP and Cav3 channels that regulates biophysical properties of a Cav3-Kv4 complex. Early behavioral results with tat-FMRP(298) introduction suggest potential therapeutic role in reducing aberrant behavioral symptoms of Fragile X Syndrome.

1-B-17 electrophysiological and firing properties of layer 2/3 and layer 5 of human tissue: in vitro study

Homeira Moradi[1], lihua wang[1], Taufik valiante[2], liang zhang[1], Peter Carlen[3]

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

Abstract We have previously demonstrated in human cortical tissue, coherent theta oscillation appear to originate from deep cortical layers, suggesting deep layer pyramidal cells likely possess distinct biophysical and active properties to drive them. To explore this hypothesis, we utilized whole-cell recording from L2/3 and L5 cells of the human neocortex, obtained from epilepsy surgery. L5 exhibited significantly different passive and active properties from L2/3. L5 cells displayed higher input resistances, greater depolarization of resting membrane potential, longer time constant, higher sag voltage amplitude, presence of a rebound spike and higher action potential amplitude with shorter half-width, in contrast to L2/3 cells. The frequency-current curve exhibited a greater firing rate and less adaptation for L5 cells. The discrepancies in the sag characteristics of the two layers indicate that the Ih-dependent resonance could also be distinctive. Both layers do not display a distinct peak in impedance at theta, although reliably follow input at theta frequencies and can track them with high fidelity. We conclude that the differences in passive and active properties result in L5 demonstrating greater excitability, including rebound spike, which may underlie its ability to drive cortical theta oscillations in human neocortex. Key word: Electrophysiological properties, repetitive firing, temporal cortex, human

1-B-18 Control of Neuroplasticity Effector Arc/Arg3.1 by Protein Lysine Acetylation

Jasmin Lalonde[1], Surya Reis[2], Sudhir Sivakumaran[3], Carl Holland[2], Hendrik Wesseling[4], John Sauld[4], Begum Alural[2], Wen-Ning Zhao[2], Judith Steen[4], Stephen Haggarty[2]

[1]University of Guelph, [2]Massachusetts General Hospital / Harvard Medical School, [3]Boston University School of Medicine, [4]Boston Children?s Hospital / Harvard Medical School

Neurons have the remarkable capacity to reorganize their structure, function, and connections in response to stimuli. Among the many signaling molecules and protein effectors found supporting these neuroplastic changes, the Activity-regulated cytoskeleton-associated protein (Arc, also known as Arg3.1) can be considered one of the central, as well as most versatile, players. Although the role of Arc in synapse biology and memory consolidation has been investigated for many years, how this single protein can contribute to various forms of neuroplasticity remains difficult to explain. Complete answer to this question will likely include the revelation of an intricate set of protein post-translational modifications that act to confer different molecular and functional specificity to Arc. As part of a chemogenomic screen that probed a mechanistically diverse library of small molecules for discovery of modulators of Brain-derived neurotrophic factor (BDNF)-induced Arc expression in primary mouse cortical neurons, we unexpectedly found evidence of Arc lysine acetylation--a previously uncharacterized post-translational modification of this protein. Here, we present a range of biochemical, proteomic, and electrophysiological data supporting the idea that Arc's protein stability and function can be strongly influenced by the acetylation of specific lysine residues. Together, our findings reveal a new facet of Arc that could be potentially exploited to control neuroplasticity for clinical applications.

1-B-19 The nucleus reuniens thalami coordinates slow oscillatory activity between the neocortex and hippocampus

Brandon Hauer[1], Silvia Pagliardini[1], Clayton Dickson[1]

[1]University of Alberta

Coordinated neural activity during sleep has a positive influence on memory processes. The slow oscillation (SO), a ~1 Hz cortical rhythm apparent during slow-wave sleep, has a demonstrated role in solidifying episodic-like memories. This may be a consequence of its dynamic coordination with a similar form of hippocampal activity, allowing for staged synchronization of widespread ensembles of neurons important for a memory trace. Effectively, the SO may be a

potential offline platform for information to be replayed between hippocampus and neocortex, allowing for consolidation. In the context of this SO circuit, we have been studying the role of the nucleus reuniens (RE) thalami, which mediates a direct connection between cortex and hippocampus. Using an optogenetic approach, we selectively stimulated RE inputs to the hippocampus and could reliably generate a hippocampal evoked response. Consistent with an important role in coordinating the two areas, multi- and single-unit recordings showed SO-correlated activity in RE cells. Crucially, when RE cells were chemogenetically inhibited, the synchronization between cortical and hippocampal sites decreased. The RE appears to be an integral part of the slow-wave memory circuit, acting as a mediator between cortex and hippocampus, especially for slow oscillatory activity.

1-B-20 Electrophysiological Profile of Differentiating Human Spinal Cord Stem Cells

Kyle Malone[1], Ahmad Galuta[2], Shawn Hayley[1], Eve Tsai[3], Michael Hildebrand[1]

[1]Carleton University, [2]University of Ottawa, [3]The Ottawa Hospital

Stem cell transplants are a promising tool for promoting regrowth after spinal cord injury (SCI). Ependymal cells comprise the SC central canal. Following SCI in rodents, they proliferate extensively and differentiate into glia and, to a lesser extent, neurons. For clinical translation, the differentiation of human spinal ependymal stem-progenitor cells (epSPCs) must be characterized. Through isolation of viable spinal tissue from organ donors, the Tsai lab has shown that human epSPCs mainly differentiate into cells staining positive for astrocytic markers, with minimal neurons. Here, we use electrophysiology to test whether immunohistochemically identified neurons exhibit a functional neuronal phenotype and to discern whether BDNF and GDNF promote neuronal differentiation. After 1 week of human epSPC culture, we used patch-clamp recordings to measure passive and active membrane properties of cells with neuron-like morphology. The resting membrane potential of cells in control and BDNF+GDNF conditions ranged from -8 to -58mV. All cells lacked action potential firing, even after 8 weeks in culture. Surprisingly, voltage-clamp recordings identified spontaneous excitatory synaptic currents at +40 and +60mV but not at -60mV. Our results suggest human epSPCs expressing neuronal markers do not exhibit a mature neuronal phenotype but develop excitatory synaptic elements early in differentiation. Identifying which factors produce functional neurons will yield a source of human spinal neurons for the study of neurodegeneration mechanisms and for potential transplant approaches.

1-B-21 A model of failed remyelination to examine the mechanisms by which remyelination protects axons

Greg Duncan[1], Brett Hilton[2], Peggy Assinck[3], Oscar Seira[1], Philip Ly[1], Ryan Hirata[4], Akash Gupta[4], Mohammad Asadi-Lari[4], Catherine Pallen[1], Jason Plemel[5], Wolfram Tetzlaff[1]

[1]University of British Columbia, [2]Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), [3]The University of Edinburgh, [4]University of British Columbia (ICORD), [5]The University of Calgary

Demyelinating inflammatory lesions are the hallmark of multiple sclerosis (MS). Myelin regeneration can occur in MS but often fails to adequately repair lost myelin leaving axons chronically demyelinated. The failure to remyelinate has been correlated with increased axonal damage. Rodent models of MS typically have effective remyelination and do not result in the chronic demyelination of axons, making it unclear if remyelination failure increases axon loss. Previously, we found that the inducible knockout of myelin regulatory factor (Myrf) from oligodendrocyte progenitor cells (OPCs) impaired remyelination following focal demytelination. Here, Myrffl/flPDGFRα CreERT2 (Myrf ICKO) and Myrffl/fl littermate controls were injected daily with rapamycin and fed a diet containing 0.3% cuprizone for six weeks to induce near complete demyelination of the medial corpus callosum. Resumption of a regular diet was used to permit remyelination. During the fifth week of cuprizone intoxication, mice were injected with tamoxifen to knockout Myrf from OPCs. OPCs from Myrf ICKO mice failed to fully differentiate resulting in little remyelination. Electron microscopy revealed that the number of large caliber axons (>1.0μm) is reduced in Myrf ICKO mice relative to controls seven weeks following the resumption of a regular diet. Myrf ICKO mice also exhibited slower recovery of motor coordination as assessed on the rotarod and Catwalk gait analysis following cuprizone intoxication. This work provides causal evidence that remyelination failure worsens axon loss and impairs locomotor recovery.

1-B-22 Resting astrocyte calcium bidirectionally regulates tonic brain blood flow

Jordan Haidey[1], Grant Gordon[2]

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

Astrocyte-mediated neurovascular coupling has conventionally been examined in the context of transient neuronally-evoked calcium events triggering phasic changes in arteriole diameter. Our research group has recently demonstrated that driving astrocyte calcium to zero elicits

prominent vasoconstriction in adjacent arterioles, suggesting that the basal astrocyte calcium level maintains resting arteriole tone; thereby controlling brain blood flow tonically. However, it is unclear how subtle fluctuations in resting astrocyte calcium may regulate vascular tone. Using two-photon fluorescence imaging and patch-clamp in acute cortical brain slices acquired from Sprague Dawley rats, we used various ratios of BAPTA and free calcium to clamp astrocyte free calcium at low (25 nM), near-resting (100 nM), and moderate (250 nM) levels, to examine any resulting changes in arteriole tone. Our preliminary data show that clamping astrocyte calcium at 25 nM increases arteriole tone (vasoconstriction), whereas clamping at 250 nM calcium decreases arteriole tone (vasodilation). In contrast, both the 100 nM calcium clamp solution and the EGTA control solution produce no substantial changes in arteriole diameter. Each calcium clamp manipulation was met with a corresponding change in resting astrocyte calcium fluorescence measured using Rhod-2. These results suggest that moderate deviations in astrocyte cytosolic free calcium from resting physiological levels may set basal vascular tone in a bidirectional manner.

1-B-23 Cholinergic neurotransmission in different subregions of the substantia nigra differentially controls DA neuronal excitability and locomotion

Jasem Estakhr[1], Danya Abazari[2], Kaitlyn Frisby[1], J. Michael McIntosh[1], Raad Nashmi[1]

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

Understanding how the substantia nigra pars compacta (SNc) dopaminergic (DA) neuronal activity governs movements requires a detailed knowledge of how different neurotransmitter systems precisely modulate DA neuronal excitability. We performed whole-cell recordings of SNc DA neurons from knock-in mice with channelrhodopsin expressed in cholinergic neurons and found a heterogeneity of electrophysiological properties between medially and laterally located SNc neurons. Lateral DA neurons received mainly excitatory mediated cholinergic neurotransmission (nicotinic or glutamatergic responses), resulting in greater neuronal excitability. However, medial SNc DA neurons received predominantly biphasic current responses consisting of GABAergic and nicotinic receptor mediated cholinergic neurotransmission, leading to a net inhibition of excitability of DA neurons at 5 Hz blue light stimulation of cholinergic terminals, while 15 Hz stimulation resulted in an inhibition followed by enhanced action potential firing. To examine whether cholinergic signaling in the SNc controls mouse behaviour, we delivered blue light through fiber optics implanted into either the medial or lateral SNc and monitored locomotion. Activation of the cholinergic system in the medial SNc

resulted in decreased locomotion, while in the lateral SNc increased locomotion. Together our findings provide new insights into how cholinergic inputs to subregions of the SNc may regulate the excitability of the DA neurons differentially, resulting in different patterns of motor behaviour.

1-B-24 Piezo1 is a novel calcium entry pathway in astrocytes

Leigh Wicki-Stordeur[1], Rebecca Ko[1], Brian MacVicar[1]

[1]University of British Columbia

Astrocytes play critical roles in regulating and supporting brain function. Although electrically unexcitable, astrocytes are well known to exhibit complex and diverse calcium sparks in response to a variety of stimuli. These calcium elevations are proposed to drive gliotransmitter release, mediating astrocytic regulation of blood flow, neuronal firing, and/or synaptic plasticity; although, the precise function of these calcium sparks remains disputed. Recent work from our lab demonstrated that calcium signals within the fine processes of hippocampal astrocytes were largely due to influx of calcium from the extracellular space, rather than release from internal stores. However, the precise pathway(s) of calcium entry remained unknown. Here we uncover a novel mechanism regulating calcium entry in astrocytes. We demonstrate expression of the Piezo1 mechanosensitive cation channel both in primary astrocyte culture, and within astrocytes in the brain. Using pharmacological approaches to modulate channel function, as well as siRNA knock-down strategies, we show that Piezo1 contributes to astrocyte calcium elevations. This work identifies a new player in astrocyte calcium signalling, and contributes to unravelling its importance within the brain.

1-B-25 Uncommonly unconscious commonalities between sleep and anesthesia

Rachel Ward-Flanagan[1], Alto Lo[1], Marissa Sobey[1], Clayton Dickson[1]

[1]University of Alberta

Sleep is a neurobiological process vital for basic physiological functions and thus, survival. Yet, despite the fundamental significance of sleep, delineating its underlying mechanisms has been slow to progress since the most common model for sleep has been sleep itself. Naturally, anaesthesia, which has direct behavioural parallels to natural sleep, such as reversible loss of

consciousness, decreased sensory awareness and reduced behavioural responsiveness, presents a potential alternative model for natural sleep. Our aim is to characterize how clinically relevant anaesthetics promote specific electrophysiological components resembling natural sleep in order to identify how anaesthesia may co-opt endogenous sleep mechanisms. The archetypical EEG dynamics of natural sleep consist of spontaneous alternations between activated and deactivated forebrain states, known as REM and non-REM sleep, respectively. These spontaneous alternations are correlated with several critical physiological functions, including modulation of respiratory activity during sleep, changes in heart rate, as well as higher order neural functions such as memory consolidation. Currently, our data suggests that only urethane shows robust spontaneous forebrain state alternations which strongly resemble the REM/nREM cycle observed in natural sleep in terms of these physiological correlates, dependence on ascending anatomical pathways, and electrographic (EEG) components and their temporal dynamics. Subsequently, urethane is the most viable anaesthetic model for natural sleep that we have assessed at present.

1-B-26 Nonlinear frequency-dependent recruitment of a slow inhibitory circuit in the raphe by habenula inputs

Michael Lynn[1], Sean Geddes[1], Sébastien Maillé[1], David Lemelin[1], Richard Naud[1], Samir Haj-Dahmane[2], Jean-Claude Beique[3]

[1]University of Ottawa Brain and Mind Institute, Centre for Neural Dynamics, [2]University at Buffalo, State University of New York, [3]University of Ottawa

The habenulo-raphe pathway is implicated in optimal behavioral responses to aversive, threatening or stressful environments. However, little is known on how long-range inputs from the lateral habenula (LHb) are processed within the dorsal raphe nucleus (DRN). Here, using optogenetic strategies in combination with whole-cell electrophysiology, we describe how repetitive optogenetic stimulation of LHb axons trigger a novel form of protracted feed-forward inhibitory processing in the DRN network, which occurs in parallel with classical monosynaptic excitatory and disynaptic inhibitory conductances. This protracted LHb-driven hyperpolarizing response lasted for seconds, its induction was steeply dependent on the frequency of LHb inputs and it 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. Moreover, this inhibitory

transmission bears features of a synaptic accumulator. Thus, this non-linear process provides the LHb inputs with the ability to outcompete parallel inputs to the DRN. More broadly, these functional connectivity features provide an effective and perhaps generalizable neural strategy to implement a dynamic input selection mechanism in hub-like networks.

1-B-27 Roles of GSK3 in Brain Anatomy and Synaptic Function

Tsukiko Miyata[1], Ariel Avila[2], John Georgiou[3], Graham Collingridge[4], Lily Qiu[5], Jason Lerch[5], James Woodgett[6]

[1]University of Toronto; Lunenfeld-Tanenbaum Research Institute, [2]Lunenfeld-Tanenbaum Research Institute, [3]Lunenfeld-Tanenbaum Research Institude, Mount Sinai Hospital, [4]University of Toronto, [5]The Hospital for Sick Children, [6]University of Toronto; Lunenf

Glycogen synthase kinase 3 (GSK3) is a serine/threonine protein kinase implicated in brain development and dysfunction. For example, GSK3 is required for neuronal differentiation and proper formation of axons. Moreover, the most commonly prescribed mood-stabilizing drug for patients with bipolar disorder, lithium, directly inhibits GSK3 activity. However, the mechanisms by which GSK3 orchestrates its effects on brain function and dysfunction are poorly understood. This study was designed to investigate the role of the two mammalian isoforms of GSK3, GSK3α and β, by conditional gene deletion in neurons of the adult mouse brain. The gene for either GSK3α or GSK3β was excised using Cre-mediated recombination, with Cre expression driven in the adult forebrain by the CAMKIIα promoter. We compared hippocampal electrophysiological and anatomical properties of GSK3-Cre knockout (KO) and control mice. Preliminary findings revealed an isoform-specific effect of GSK3 suppression on synaptic plasticity and hippocampal volumes such that the hippocampus in GSK3α-Cre KO mice, but not GSK3β-Cre KO mice, was larger in size and exhibited impaired induction of long-term potentiation and long-term depression, as compared to control slices. These findings support the idea of specific functions of GSK3 isoforms on adult hippocampal volume and synaptic plasticity in an adult excision model where early neurodevelopmental effects are unlikely to confound conclusions. Ongoing work is examining pharmacological inhibition of GSK3 as well as behavioural analyses to measure functional changes.

1-B-28 The verified channelome of the rat subfornical organ

Colleen Peterson[1], Alasatir Ferguson[2], William Fry[1]

[1]University of Manitoba, [2]Queen's University

The subfornical organ (SFO) is small forebrain sensory circumventricular organ (sCVO). Due to the unique absence of a blood-brain barrier in these regions, and their synaptic connections to and from homeostatic control centre, sCVOs are critical for homeostasis. The ability of the SFO to detect and transduce circulatory signals is mediated by the population of ion channels and G-protein-coupled receptors (GPCR) expressed. To identify the ion channelome and GPCR transcriptome of the SFO, we performed Illumina whole transcriptome sequencing on SFO tissue from Sprague Dawley rats aged six weeks. Read sequences were aligned to the Rat Rnor 6.0 genome and annotation, and FPKM calculated using Stringtie. Transcript frequency was compared to a previously published intensity values from published microarray data from Hindmarch et al. for validation. To identify ion channels and GPCRs, both datasets were compared to the IUPHAR Guide to Pharmacology target database. Ninety-six voltage-gated ion channels, 50 ligand-gated ion channels, 25 other ion channels, and 193 GPCRs were identified by RNA sequencing. These include 58 voltage-gated ion channels, 31 ligand-gated ion channels, 12 other ion channels, and 119 GPCRs which were not previously detected by microarray. We present here a channelome dataset which may serve as an important resource for further studies of ion channel and GPCR function in the SFO.

1-B-29 Astrocyte coupling and lactate shuttle deficits underlie long-term plasticity impairments after acute stress

Ciaran Murphy-Royal[1], Jaideep Bains[1], Grant Gordon[1]

[1]Hotchkiss Brain Institute, University of Calgary

Although much is known regarding neuron-glia interactions under physiological conditions, our understanding of how the functional relationships between astrocytes and neurons adapt to physiological and pathological challenges is limited. Here we set out to investigate how acute stress impacts astrocytes and their relationship with neurons. Using 2P microscopy and electrophysiology we observed that stress affects astrocyte structure and function leading to: increased cell size and complexity, modified intrinsic calcium signalling, and reduced gap-junction coupling. Glucocorticoid receptor signalling was both necessary and sufficient for these effects: In naïve slices, CORT application reproduced the impairments in gap-junction coupling; blocking CORT synthesis in vivo prior to stress attenuated the stress-induced reduction in gap-

junction coupling. Due to the importance of gap-junction coupling in energy substrate shuttling, we hypothesised that impaired astrocyte coupling could impact neuronal function, resulting in an energy deficit at the synapse. Supporting our hypothesis, we observed a stress-induced impairment in long-term potentiation (LTP), which was rescued by supplementing astrocytes with physiological concentrations of intracellular L-lactate. This reveals that astrocyte gap-junction dysfunction and the delivery of lactate, at least in part, underlies the neuronal LTP deficits induced by stress. These data implicate astrocytes as mediators of the central stress response, warranting further investigation of the roles of these cells in stress-related pathology

1-B-30 Prenatal Ethanol Exposure has Sex-Specific Impact on the Dynamic Range of Hippocampal Synaptic Plasticity

Christine Fontaine[1], Cristina Pinar[1], Waisley Yang[1], Angela Pang[1], Brian Christie[1]

[1]University of Victoria

Ethanol is a teratogen and Prenatal ethanol exposure (PNEE) can lead to a spectrum of neuropathology known as Fetal Alcohol Spectrum Disorders (FASDs). FASD is characterized by impaired cognitive functioning that includes reduced learning and memory performance. Similarly, PNEE has been shown to impair long-term potentiation (LTP) of synaptic plasticity, a biological model for learning and memory mechanisms. However, no studies have examined how PNEE affects long-term depression (LTD) of synaptic efficacy and the dynamic range of both forms of synaptic plasticity. These experiments were performed by administering an ethanol-containing liquid diet to pregnant female rats throughout gestation, and then performing in vitro electrophysiology in the offspring. Specifically, we examined both LTP and LTD in the dentate gyrus of juvenile male and female Sprague-Dawley rats from both PNEE and Control litters. Our results indicate that following PNEE juvenile male and female animals have a reduced capacity for LTP in the DG. In contrast, we observed a sex-specific reduction in the magnitude of LTD selectively in PNEE males but not in females. These differences were abolished if LTD was saturated with prolonged low-frequency stimulation, indicating the basic molecular machinery required for LTD remains functional. In both sexes the dynamic range for LTP and LTD was reduced when compared to control animals, indicating that PNEE reduces synaptic flexibility in the offspring that is apparent during a period that is normally characterized by enhanced synaptic plasticity.

1-B-31 Regional specialization of the Blood-Brain Barrier

Marie Blanchette[1], Nadine Ruderisch[2], Richard Daneman[1]

[1]University of California, San Diego, [2]Abbvie

The blood-brain barrier (BBB) consists of a set of properties expressed by brain endothelial cells (BEC), including a high expression of tight junction molecules and specific transporters, low rates of trancytosis and a low expression of leucocyte adhesion molecules. These properties allow a tight regulation of the ions, molecules and cells moving across the BBB. The specific transporters expressed at the BBB control the entrance of specific nutrients and signaling factors, mandatory for proper brain function. The different regions of the CNS are composed of different neuronal suggesting that different regions of the brain may need different levels nutrients, neurotransmitter precursors or signaling factors to achieve proper neurological functions. However, it is not known if there are regional specializations of the BBB required to locally regulate brain properties. In order to determine if there is a regional specialization of the BBB, we performed RNA sequencing on BECs isolated from the forebrain, cerebellum and spinal cord. The different expression of BBB specific genes was compared between the three different isolated CNS regions. We found multiple genes and pathways enriched at the BBB in each CNS region. We are now exploring their function at the BBB and how they regulate proper brain function. These data suggest that the BBB has fundamental basic characteristics but also has certain heterogeneity to fulfill the specific needs of each brain regions. This opens a whole new field of research as the BBB was thought to be specific properties displayed by all BECs.

1-B-32 Molecular mechanisms of Irisin-induced turning response at developing motoneuron.

Jau-Cheng Liou[1]

[1]National Sun Yat-Sen University

It is well known that irisin, the cleaved fragment of the transmembrane protein type-III domain containing protein 5 (FNDC5), is an exercise induced myokine that is involved in the regulation of adipose browning and thermogenesis. Recent studies have uncovered some important biological functions of irisin in nervous system. For example, irisin regulates depressive-like behavior, induces neural differentiation of embryonic stem cell and protects against oxygen-glucose-induced neuronal injury. In this study, we focused on the possibility and underlying molecular mechanisms of irisin in the guidance of a developing neuron by using primary

cultured developing motoneurons of Xenopus laevis. The chemical gradient of irisin on a growth cone can be achieved through pressure-derived irisin ejection from a micropipette at 1 Hz in frequency, 50 msec in duration. Although the growth rate of developing axons was not significantly affected, irisin elicits a significant attraction on the guidance of the growth cone. Neither growth rate nor direction of the growth cone was affected in the presence of irisin R75E, a glutamate substitution in the functional domain of irisin. The irisin-induced attractive guidance effect was abolished when calcium was eliminated from the culture medium, suggesting an influx of calcium is responsible for irisin-induced turning response. Pretreatment of IP3 receptor inhibitor (XeC) effectively occluded growth cone turning response induced by irisin. In addition, pretreatment of ryanodine receptor inhibitor (TMB-8、Ruthenium red) also effectively to occlude growt

1-B-33 TLR4-mediated increase of microglial glycolysis inhibits expression of LTP through IL-1b

Elisa York[1], Jingfei Zhang[1], Hyun Choi[1], Rebecca Ko[1], Jeff LeDue[1], Brian MacVicar[1]

[1]University of British Columbia

Microglia are critical for maintaining brain health. However, during immune activation, they also contribute to altered brain function, neurotoxicity, and degeneration. In peripheral immune cells, activating stimuli increase glycolysis, while anti-inflammatory polarization enhances oxidative phosphorylation. Therefore, we investigated whether microglia also become dependent on glycolysis following an immune challenge, and whether blocking the glycolytic pathway weakens pro-inflammatory responses. Here, we establish the use of fluorescence lifetime imaging (FLIM) of endogenous NADH to investigate the metabolic state of microglia and neuropil in acute hippocampal slices. While neuropil tissue is affected by anoxia or aglycemia, microglial cells maintain a stable NADH signal throughout these manipulations, suggesting a rapid metabolic flexibility. This unique NADH FLIM signal in microglia suggests that metabolic pathways may be markers of microglial immune activation or quiescence. Following lipopolysaccharide (LPS) stimulation of TLR4 receptors, microglial cultures increased production of the pro-inflammatory cytokine, interleukin-1b (IL-1b), which was blocked by treating cultures with a-ketoglutarate. In acute hippocampal field recordings, LPS stimulation and IL-1b release impairs long term potentiation. This effect can be rescued by the IL-1b receptor antagonist or by inhibiting glycolysis. These results suggest a link between inflammation and cognitive deficit, and implicate cellular metabolism as a potential mediator of microglial function.

1-B-34 It's about time: PKA-dependent LTP integrates the timing of stimuli via LIMK1

Sammy Cai[1], Graham Collingridge[1], Zhengping Jia[1]

[1]University of Toronto

Long-term potentiation (LTP) has been studied extensively to understand the molecular mechanisms underlying learning and memory. The NMDA receptor-dependent form of LTP can be characterized into protein kinase A (PKA)-dependent and independent forms depending on the spacing between theta burst stimuli (TBS). Compressed (c)TBS does not require PKA whereas spaced (s)TBS elicits a PKA-dependent form that requires the insertion of calcium permeable AMPA receptors (CP-AMPAR) (Park et al [2016] J Neurosci.). The PKA-dependent form of LTP has implications in protein translation that may alter the molecular composition, structure, and function of synapses; however, the mechanism by which synapses integrate the timing of stimuli remains elusive. To investigate these processes, we have used electrophysiology to compare cTBS and sTBS at mouse CA1 synapses using genetic knockout (KO) or pharmacological inhibition of the PKA pathway. We found that LTP induced by sTBS was sensitive to inhibitors of PKA and protein synthesis. Mice lacking LIM kinase-1 (LIMK1), a potent regulator of actin cytoskeleton dynamics, revealed deficits in PKA-dependent LTP, and was insensitive to protein synthesis inhibitors applied throughout sTBS. Preliminary results suggest that PKA can activate LIMK1 to trigger protein synthesis-dependent pathways critical for plasticity. These findings provide insight into how spaced stimuli can be consolidated into long-term memories.

1-B-35 Discovering novel Ankyrin B interactions and understanding its role in neuronal function

Catherine Choi[1], Laura Arbour[2], Leigh Anne Swayne[1]

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

Ankyrin B (AnkB) is a scaffolding protein for ion channels and receptors. Mutations in AnkB are known to cause human diseases in the heart. AnkB has also been shown to play a key role in the development of the nervous system and has been shown to interact with a handful of key neuronal proteins, but it's role is not yet fully understood. To better understand the role of AnkB in neurons, we used an unbiased mass spectrometry approach to identify the AnkB interactome

in neural cells. We have identified 40 proteins that co-immunoprecipitated with human AnkB expressed in Neuro2a cells (a neuroblastoma cell line). Many of these novel hits are related to the cytoskeleton; more specifically, they are involved in the regulation of actin dynamics. In addition to this unbiased screen, we have also taken a parallel targeted approach that focuses on knowledge gaps in our understanding of the interaction of AnkB with the presynaptic P/Q-type voltage gated calcium channel pore-forming subunit, Cav2.1. Our preliminary results suggest that AnkB increases Cav2.1 surface expression. Notably, reduced Cav2.1 surface expression was observed in cells expressing disease-associated AnkB variants (including one recently identified by our group). The discovery of novel AnkB interaction and understanding how AnkB affects the function and localization of these proteins will provide valuable insight into neuronal and synaptic development.

1-B-36 ATP-induced endocytosis of Pannexin 1: molecular mechanisms

Andrew KJ Boyce[1], Leigh Anne Swayne[2]

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

Pannexin 1 (Panx1) is an ATP release channel that is enriched in the nervous system. Although Panx1 research has focused primarily on its function at the cell surface, it is also readily detected on intracellular membranes. ATP is continuously released from several neural cells types (via exocytosis and channels like Panx1) and activates P2 purinergic receptors that physically and functionally couple to Panx1. We initially investigated the hypothesis that extracellular ATP is linked to the intracellular expression of Panx1, demonstrating that elevated extracellular ATP induces robust Panx1 endocytosis (Boyce et al. 2015). In subsequent work, we followed up on the key observation that this phenomenon is sensitive to a highly-selective blocker for the P2X7 receptor (P2X7R). In our second study (Boyce et al. 2017), we discovered that ATP facilitates physical interaction between the P2X7R and Panx1, followed by endocytosis of P2X7R-Panx1 clusters. Our additional published and unpublished work has further revealed that endocytosis occurs via macropinocytosis, a regulated form of cholesterol-dependent endocytosis. These discoveries provide additional insight into P2X7R-Panx1 crosstalk as well as the first evidence that Panx1 distribution is responsive to changes in the cellular environment. This work also raises the important possibility that Panx1-associated behaviours could be regulated by modulation of protein trafficking in response to changes in extracellular ATP.

1-B-37 Lack of novel current in NALCN-transfected HEK-293 cells

Mark Fry[1], Colleen Peterson[1], Jennifer Egan[1]

[1]University of Manitoba

The nonselective cation channel NALCN is an ion channel responsible for tetradoxin-resistant sodium leak current, and is reported to regulate resting membrane potential and electrical excitability. Although the mechanism of NALCN activation remains unclear, previous work has indicated that NALCN currents can be stimulated by activation of several G protein coupled receptors, including the M3 muscarinic receptor (M3R) in pancreatic â- and HEK-293 cell lines. To investigate M3R-activated NALCN currents, HEK-293 cells were transfected with eGFP, M3R, or NALCN and its accessory proteins (UNC80 and Src), and muscarinic agonist-activated currents recorded from them and untransfected HEK-293 cells. No significant differences were observed between the groups before or after muscarine or oxotremorine-M application. Thus our findings do not support the previous studies which suggest that NALCN forms a functional sodium leak channel in HEK-293 cells. More research is required to determine the molecular requirements for the successful heterologous expression of the NALCN channel.

1-B-38 The role of endogenous cellular prion protein in brain synaptic function

Aeen Ebrahim Amini[1], John Georgiou[2], Changiz Taghibiglou[3], Graham Collingridge[1]

[1]University of Toronto, [2]Lunenfeld-Tanenbaum Research Institude, Mount Sinai Hospital, [3]University of Saskatchewan

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) are the major neurotransmitter receptors in the brain that are involved in glutamate-based neuronal communication. Increases and decreases in AMPAR number, distribution, and efficacy represent some of the mechanisms that neurons employ to modulate their communication strength, which is known as synaptic plasticity. Defects in synaptic plasticity may be responsible for many brain disorders including Alzheimer's disease (AD). It has been shown that beta-amyloid oligomers bind the cellular prion protein (PrPC), a cell-surface glycoprotein with many physiological functions such as cellular differentiation, adhesion and control of cell morphology. However, the role of PrPC in synaptic plasticity and learning and memory remains obscure. We used electrophysiological techniques to explore the function of PrPC at CA1 synapses in the hippocampus, a region critical for learning and memory and preferentially affected in AD. Preliminary data suggest that C57BL/6J-Prnp knockout mice have enhanced long-term

potentiation. The input/output function of synaptic transmission and paired-pulse potentiation were unaffected. Ongoing investigations will confirm these initial findings and examine the role of glutamate receptors in PrPC-dependent modulation of synaptic plasticity. We conclude that PrPC may serve to limit synaptic potentiation.

1-B-39 Pannexin 1: a novel regulator of dendritic spine development in the postnatal cerebral cortex

Juan Sanchez-Arias[1], Olga Shevtsova[1], Mei Liu[1], Maria Weaver[1], Leigh Anne Swayne[1]

[1]University of Victoria

Pannexin 1 (Panx1) is a channel-forming protein that is enriched in the nervous system. We previously reported that disruption of Panx1 was associated with increases in the number and length of neurites in vitro. Notably, Panx1 mRNA levels in the cerebral cortex peak around birth and then drop off rapidly. Our new findings confirm Panx1 protein expression drops dramatically between P14 and P30 corresponding with the critical period for cortical dendritic spine and synapse formation. Here we investigated the hypothesis that Panx1 "keeps the brakes" on dendritic spine formation in the cerebral cortex. We first examined the impact of disrupting Panx1 (block with probenecid or KO) on primary somatosensory cortex layer 5 dendritic spine density and length in the postnatal period using diolistic labeling. We observed an increase in spine density, suggesting Panx1 negatively regulates spine development in vivo in the postnatal cerebral cortex. Similarly, Panx1 KO was associated with increased spine density. To investigate the functional consequences associated with Panx1 disruption in cortical neurons, we used a combination of Ca2 imaging, immunostaining and immunoblotting for markers associated with functional synapses, followed by behavioural analysis of sensorimotor function. Disruption of Panx1 altered Ca2 dynamics and increased markers of mature synapses. As follows, Panx1 KO mice exhibited superior sensorimotor function to WT controls. Together, these results establish Panx1 as a novel modulator of developmental plasticity in the brain.

1-B-40 Longitudinal imaging of thalamocortical axon dynamics reveals central diabetic neuropathy

Eslam Mehina[1], Craig Brown[1]

[1]University of Victoria

Diabetes mellitus is commonly associated with the loss of peripheral nerve fibers leading to sensory impairments (tingling, numbness, pain) and motor abnormalities. Although the degeneration of peripheral nerves contributes to symptoms of sensory loss and motor issues in diabetes, early changes in upstream somatosensory pathways have not been well characterized. We hypothesized that diabetes mellitus affects sensory-related circuits in the central nervous system. In particular, we focused on thalamic axonal projections to the primary forelimb somatosensory cortex, a relay critical for transducing sensory information from the periphery into cortically perceived sensation. Here we used two-photon microscopy to follow changes in GFP-labelled thalamocortical synaptic boutons in hyperglycemic diabetic mice and healthy controls over 15 weeks. In non-diabetic animals, turnover rates for thalamocortical en passant boutons were steady over time with comparable rates of bouton gain and loss. By contrast, turnover rates were elevated in diabetic mice and characterized by greater rates of bouton gain relative to loss. By tracking the lifespan of synaptic boutons, we discovered that newly formed boutons were less likely to survive (persist over a 3 week period) in the diabetic brain, but a fraction of pre-exisiting boutons (those present prior to the onset of hyperglycemia) were relatively unaffected. Together these findings enhance our understanding of the underlying structural changes that may contribute to the manifestation and progression of sensory loss in diabetes mellitus.

1-C-41 Suppressing interferons reinvigorates microglial repair of microbleeds in the diabetic brain

Stephanie Taylor[1], Eslam Mehina[1], Emily White[1], Kristian Doyle[2], Patrick Reeson[1], Craig Brown[1]

[1]University of Victoria, [2]University of Arizona

Microcirculatory damage is a common complication for those with vascular risk factors such as diabetes. In order to resolve vascular insults, the brain's innate immune cells, microglia, must rapidly envelop and repair the site of injury. Currently it is unknown whether type 1 diabetes, a condition associated with chronic immune system dysfunction, alters microglial responses to damage and what mechanisms are responsible. Using in vivo 2-photon microscopy, we show that microglial envelopment of laser induced cerebral microbleeds (CMB) is diminished in a hyperglycemic mouse model of type 1 diabetes, which could not be fully reversed with chronic insulin treatment. Microglia were important for vessel repair since reduced microglial accumulation in diabetic mice or near complete depletion in healthy controls was associated

with greater secondary vessel leakage. Broadly suppressing inflammation with dexamethasone (DEX) in diabetic mice but not healthy controls, significantly improved microglial responses to CMB and attenuated secondary vessel leakage. These improvements were associated with changes in interferon (IFN) signalling since DEX suppressed abnormally high levels of IFNá and ã protein levels in diabetic blood serum. Further, reducing IFNá receptor-1 signalling and to a lesser degree IFNgamma with neutralizing antibodies was sufficient to normalize microglial responses and vessel repair in diabetic mice. These results show that IFN targeting immunotherapies can stimulate microglial repair of vascular insults in the diabetic brain.

1-C-42 High-throughput phenomic characterization of ASD-associated genes reveals a functional gene network underlying hypersensitivity and impaired habituation

Troy McDiarmid[1], Manuel Belmadani[1], Fabian Meili[1], Kurt Haas[1], Paul Pavlidis[1], Catharine Rankin[1]

[1]University of British Columbia

A primary challenge facing Autism Spectrum Disorder (ASD) genetics 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 characterized 26 quantitative phenotypes spanning morphology, locomotion, sensory, and habituation learning in 97 strains of C. elegans each carrying a mutation in an ortholog of an ASD-associated gene. This research has generated a large number of novel genotype to phenotype relationships that range from severe developmental delays and uncoordinated movement to subtle deficits in sensory and learning behaviours. Clustering based on multi-parametric phenomic profiles revealed a set of 12 genes that all result in a strikingly similar profile characterized by hypersensitivity and impaired habituation learning. Current epistasis experiments are aimed at determining whether the phenomic similarity among members of this cluster results from previously undiscovered functional interactions. One of the genes in this cluster is the sole C. elegans ortholog of neuroligins, nlg-1. Transgenic pan-neuronal expression of human NLGN3 in nlg-1 mutant C. elegans rescued their sensory and learning impairments; confirming functional conservation. The wealth of in vivo phenomic functional data generated in this work will inform more targeted studies in vertebrates and offers novel positive and negative pathway components as therapeutic targets for ameliorating the effects of ASD.

1-C-43 White Matter Tract Alterations in Drug-naive Parkinson's Disease Patients with Impulse Control Disorders

Mahtab Mojtahed Zadeh[1], Farzaneh Ghazi Sherbaf[1], Mohammad Hadi Aarabi[1]

[1]Tehran University of Medical Sciences

Background: impulse control disorders (ICDs) are relatively frequent in patients with Parkinson's disease (PD), mainly in those taking dopaminergic drugs, although it is still unclear whether an underlying pathological process plays significant roles in the development of impulsive-compulsive behaviors (ICB). Methods: Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmiinfo.org/data). Diffusion MRI was conducted in 93 cased divided into three groups of de-novo PD patients to find detectable white matter abnormalities between groups with or without ICB and healthy control. Groups were matched according to age at the time of diagnosis, gender, handedness, duration of disease, HY stage, UPDRS III, and MOCA score. Diffusion MRI connectometry was used to carry out group analysis between matched PD patients with and without ICB and healthy control. Results: Compared with PD no-ICB, PD-ICB cases showed decrease quantitative anisotropy (QA) in corpus callosum, left cortico thalamic, left cerebellum, right cingulum, and left cingulum(FDR=0.002). Compared with controls, allpatients had an increased QA in the corpus callosum, left corticothalamic, left cerebellum, and right cortico thalamic with increased connectivity related to group(FDR=0.001). Conclusions:PD-ICB is associated with a disconnection between midbrain, limbic, brainstem, and cerebellum. Also, Difference in QA between PD-ICB and PD no-ICB patients reflects microstructural differences may secondary to ICD.

1-C-44 Revisiting the Sygen© data using data mining methods reveals the dose dependency of efficacy of the GM-1 ganglioside in Spinal Cord Injury (SCI) patients

Navid Khosravi-Hashemi[1], Fred Geisler[2], John Kramer[1]

[1]University of British Columbia, [2]Rush-Copley Medical Center

Sygen© (monosialotetrahexosylganglioside GM1 sodium salt) is a naturally occurring compound in the cell membranes of nervous system. In a randomized, double-blind, multicenter clinical trial study, despite seemingly beneficial effects of Sygen© in SCI patients, the efficacy of the drug was not proven. While the data was collected in three treatment groups-placebo, low-dose Sygen©, and high-dose Sygen©-, no comparison between the low and high dose Sygen© treatment outcomes were reported. We revisited the data to explore if there are different

patterns of recovery among patients and if so what are the characteristics of each recovery class. We developed a data driven classification method and applied it to the American Spinal Injury Association (AISA) motor scores measured at different times following SCI. The method constituted of linear interpolation curve fitting, calculation of areas under the fitted curves, and finally applying an unsupervised machine learning clustering method called "K-means" to the computed areas. This way we were able to objectively classify the patients to three groups: little to no recovery, slow recovery, and fast recovery. By comparing the treatment groups we found that while the patients in low-dose Sygen© treatment group were distributed in recovery classes similar to the placebo treatment group, the distribution of patients in High-dose Sygen© treatment group showed a clear shift from slow recovery to fast recovery class. These results suggest that only the high-dose Sygen© treatment improves the chance of fast-recovery in SCI patients.

1-C-45 Antidepressant Effects of Transcranial Direct Current Stimulation (tDCS) in Adolescent and Adult Rats

Shannon Waye[1], Joshua Dean Conway[1], Lucas Walters[1], Francis Bambico[1]

[1]Memorial University of Newfoundland

Olfactory bulbectomy (OBX) is a rodent model of depression that results in behavioural and neurochemical changes that can be reversed by antidepressants. However, in human adolescents, antidepressant drugs often prove ineffective and may worsen symptoms (Vitiello et al. EOP, 2016). A potential solution is transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique that sends weak electrical current through the scalp to induce plasticity. We developed a rodent model of tDCS, and found that it decreased passivity and anhedonia-like behaviour in the forced swim test and fruit loop consumption test in adult rats. Experiments investigating the pro-depressive effects of OBX are under way. In adolescent OBX rats, we are currently investigate whether chronic use of fluoxetine results in worsening of depressive-like symptoms. More importantly, we will test if tDCS administered during adolescence can reduce depressive-like immobility in the forced swim test and hyperactivity in a novel, open field chamber. We will examine if this effect is achievable with tDCS alone or with adjunct fluoxetine treatment. Finally, we will examine 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 the hippocampus for ELISA analysis. Based on our previous study, we expect that both OBX surgery and chronic fluoxetine

treatment will increase passivity and hyperactivity in adolescent rats, and that tDCS will reverse these effects.

1-C-46 Neuregulin-1 fosters a pro-regenerative response by microglia and regulatory T cells in demyelinating conditions

Ghazaleh Mohammadzadeh Shahriary[1], Hardeep Kataria[2], Arsalan Alizadeh[2], Thomas K. Santhosh[1], Soheila Karimi-Abdolrezaee[2]

[1]Regenerative Medicine Program, Department of Physiology and Pathophysiology, University of Manitoba,, [2]University of Manitoba

In demyelinating conditions, activated resident microglia and infiltrating leukocytes initiate a pro-inflammatory immune response resulting in oligodendroglial death and myelin damage. We have shown that the neuronally-derived growth factor, neuregulin-1, is acutely reduced in demyelinating lesions of the spinal cord. Here, we aimed to unravel the ramification of Nrg-1 dysregulation on immune response using in vivo and in vitro models. We induced focal demyelination in dorsal spinal cord by lysolecithin (LPC). Recombinant human (rh) Nrg-1ß1 was infused intraspinally in a sustained manner using polylactic-co-glycolic acid (PLGA) microparticles for 3, 7 and 14 days. Primary microglia cultures were activated with IFN-γ and TNF-α, and treated with rhNrg-1ß1 for 24 and 72 hours. We utilized immunohistochemistry, western blotting, and Real-Time PCR to determine the effects of Nrg-1 on neuroinflammatory processes in vivo and in microglia culture. In LPC focal demyelinating lesions, Nrg-1 therapy promoted a pro-regenerative phenotype in microglia and regulatory T cells characterized by increased IL-10 and FoxP3 expression. Inactivated microglia culture, Nrg-1 similarly elicited a significant increase in IL-10 expression while attenuating the expression of pro-inflammatory mediators, TNF-α, IL-6, CD86, CCL8, CXCL2 and nitric oxide (NO). Hence, our findings suggest that Nrg-1 therapy could be exploited to foster a pro-regenerative immune response supportive of remyelination in CNS demyelinating lesions. This work is supported by the CIHR and MS Society of Canada.

1-C-47 Neural adaptations in Parkinson?s Disease for complex locomotion

Trina Mitchell[1], Alexander Thiel[1], Oury Monchi[2], Caroline Paquette[1]

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

Our aim was to determine whole-brain cerebral glucose metabolism (rCGM) of locomotor networks for complex walking in Parkinson's Disease using [18F]-fluoro-deoxy-glucose positron emission tomography ([18F]-FDG PET) during an upright walking paradigm. To this end, seven healthy control (NC, 4 females, age range: 55-63) and ten Parkinson's Disease (PD, 2 females, age range: 58-72, H&Y 2-3, withdrawn from dopaminergic medication) subjects without cognitive impairment were included. rCGM of [18F]-FDG was measured on two occasions, during steering (i.e., complex) and straight walking, performed continuously during the radiotracer uptake period. Task associated change in rCGM was compared between groups using a flexible factorial design, $p<0.005$(uncorr). During steering, NC had increased rCGM in the superior parietal lobule (SPL), superior frontal gyrus, middle occipital gyrus, and cerebellum as compared to straight walking. PD subjects had increased rCGM in similar regions for steering, however compared to NC, rCGM was reduced in the SPL, middle frontal gyrus, caudate, and cerebellum during steering. Both groups had increased rCGM of the supplementary motor area for straight walking as compared to steering, which was significantly more pronounced in NC. PD subjects show reduced rCGM bilaterally within the executive corticostriatal loop involved in complex locomotor control. These results suggest that there is an inability to recruit normal corticostriatal circuitry for complex locomotion and may represent an alternate mechanism used to compensate for motor impairments.

1-C-48 Age-Dependent White Matter Inflammation and Cognitive Impairment in the TgAPP21 Rat Model of Alzheimer Disease

Alexander Levit[1], Brian Allman[2], Nagalingam Rajakumar[1], Vladimir Hachinski[3], Shawn Whitehead[2]

[1]University of Western Ontario, [2]Western University, [3]London Health Sciences Centre

White matter pathology and executive dysfunction may be important early predictors of Alzheimer disease (AD). Both of these predictive factors have been observed in the transgenic (TgAPP21) Fischer344 rat model, which expresses a pathogenic human amyloid precursor protein (hAPP). To characterize the temporal relationship between white mater pathology and cognitive changes, male wildtype (Wt) and TgAPP21 rat behaviour and brain tissue was evaluated at 4, 8, 13, and 22 months of age. Behavioural flexibility, learning, memory, and anxiety were assessed using an operant-chamber based set-shifting task, the Morris Water Maze, and the Open Field test. Prior to learning and memory impairments, TgAPP21 developed regressive impairments in behavioural flexibility at 8 months of age. Brain tissue was analyzed

for microglia activation (OX6), which revealed significantly accelerated white matter microglia activation in TgAPP21 rats, such that 13-month-old TgAPP21 rats had as much microglia activation as 22-month-old Wt rats. White matter astrocyte activation (GFAP) was not affected by genotype. Precocious cognitive changes and accelerated white matter inflammation in the TgAPP21 rat model supports further investigation of white matter inflammation and behavioural inflexibility in prodromal AD.

1-C-49 Correlating white matter changes to executive dysfunction in a rat model of mediodorsal thalamic stroke

Jessica Snyder[1], Brian Allman[1], Shawn Whitehead[1]

[1]Western University

Recent literature has strongly supported a relationship between vascular disease in the progression of cognitive impairment. Previous studies have demonstrated that inflammation in the white matter of the brain is a pathological outcome following stroke and is highly predictive of post-stroke cognitive impairment. Moreover, previous work in our lab has demonstrated, using a rodent model of striatal stroke, that white matter inflammation (WMI) is correlated with post-stroke cognitive impairment. The current study aimed to further investigate the role of WMI in post-stroke cognitive impairment by utilizing a focal mediodorsal thalamic stroke model in the rat. Unilateral stroke in the mediodorsal thalamus was produced using an injection of the potent vasoconstrictor endothelin-1. Behavioural flexibility was assessed in these animals using an operant set-shifting task as a measure of executive function, followed by post-mortem immunohistological analyses to assess neuroinflammation. Results show that unilateral mediodorsal thalamic stroke produced increased WMI as well as a concomitant behavioural phenotype whereby these animals displayed less behavioural flexibility in comparison to controls. These findings further reinforce the proposed role of WMI in mediating post-stroke cognitive impairment and provide a strong rationale for the use of anti-inflammatory treatment to prevent white matter inflammation and preserve cognition post-stroke.

1-C-50 White Matter Hyperintensities: A combined post mortem 7T MRI and histological study of microvascular and inflammatory changes

Austyn Roseborough[1], Kristopher Langdon[1], Robert Hammond[1], Stephen Pasternak[1], Ali Khan[1], Shawn Whitehead[1]

[1]Western University

White matter hyperintensities (WMH) in magnetic resonance imaging (MRI), are considered markers of cerebral small vessel disease (SVD) in normal aging as well as in conjunction with cerebrovascular and neurodegenerative processes. WMH are areas of increased signal intensity seen on T2 and fluid-attenuated inversion recovery (FLAIR) weighted MRI sequences. WMH are associated with cognitive decline, specifically affecting executive function. The etiology of WMH is not well understood but proposed mechanisms include inflammation, edema, blood brain barrier dysfunction, gliosis and demyelination. Using 7 Tesla post mortem MRI we have identified periventricular WMH in 20 human brains from individuals with a neuropathological assessment ranging from normal to Alzheimer's Dementia and cerebrovascular disease. Periventricular white matter corresponding to hyperintense areas on MRI were sampled for histological analysis. Vascular, reactive and inflammatory findings were characterized by morphological changes to arterioles and venules, gliosis and microglial activation. Following co-registration between histology and MRI, these findings were further assessed across diagnostic categories. Our study will help improve the understanding of processes underlying chronic vascular, reactive and inflammatory injuries to white matter, a therapeutic target that may precede cognitive decline by decades and share co-morbidly with many neurodegenerative conditions.

1-C-51 Assessing Cardiac Dysfunction Post-Stroke in the Insular Cortex Ischemic Stroke Rat Model

Victoria Jaremek[1], Brittany Balint[1], Victoria Thorburn[1], Maryse Paquet[1], Jamie Melling[1], Luciano Sposato[1], Shawn Whitehead[2]

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

Patients who have suffered an ischemic stroke with damage to the right insular cortex (IC) may develop secondary myocardial injury. However, the pathophysiology and time course of these post-stroke cardiac changes require further investigation which is complicated by lack of pre-clinical models. The purpose of this work is to establish a pre-clinical model of selective insular cortical stroke to evaluate post-stroke cardiac effects. To do this, IC ischemic stroke was induced in 6-month-old male Wistar rats via unilateral stereotaxic injection of endothelin-1 into right IC.

Hearts were histologically examined at 28 days post-stroke for fibrosis (Masson's Trichrome stain), inflammation (CD45+, myeloperoxidase, CD3+, CD45R, CD68+ immunostaining) and endothelial dysfunction (phosphorylated endothelial nitric oxide synthase). Further, to establish a time course of cardiac dysfunction, same rat model was used with hearts examined at 6, 24 hours, 7, 14 and 28 days post-stroke in areas of interest (4 heart chambers and pulmonary vein/left atrium border (PV-LA border)). Results from this study showed that focal IC stroke led to left atrial and PV-LA border tissue fibrosis, inflammation and endothelial dysfunction 28 days post-stroke. Preliminary results from the time course demonstrate increased PV-LA border tissue fibrosis at 14 and 28 days as well as increased left atrial tissue fibrosis at 7 and 14 days. These findings provide insight into the progression of post-stroke cardiac changes and suggest that inflammation is a treatable target to prevent cardiac changes post-stroke.

1-C-52 Development of an Insular Ischemic Stroke Animal Model to Study the Pathophysiology of Atrial Fibrillation Detected after Stroke (AFDAS)

Victoria Thorburn[1], Brittany Balint[1], Maryse Paquet[1], Luciano Sposato[1], Shawn Whitehead[2]

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

Atrial fibrillation (AF) increases risk of ischemic stroke 5-fold. Recent evidence suggests that stroke can generate AF. While it is thought that stroke involving the insular cortex (IC) initiates AFDAS, exact mechanisms remain unknown. We hypothesize AFDAS is the consequence of IC damage occurring after stroke, which disrupts autonomic regulation of heart rhythm. As a first step of an overall initiative to evaluate the pathophysiology of AFDAS, we aimed to create a rat model of focal insular ischemic stroke. Stroke was induced into the right (n=8) or left (n=8) insular cortex of 6-month-old male Wistar rats through stereotaxic injection of endothelin-1. Control groups received saline injection (n=7 right IC / n=7 left IC) or no injection (n=6). Heart tissue was analyzed for left atrial fibrosis (LAF) and brain tissue analyzed for neuroinflammation at 28 days post-stroke. LAF was greater in animals with right IC stroke (5.8±1.2%) compared to right IC saline injection (0.6±0.1%; p=0.021) and no injection (0.6±0.1%; p=0.004) controls, as well as in animals with left IC stroke (4.5±1.3%) compared to left IC saline injection (0.7±0.1%; p=0.020) and no injection (0.6±0.1%; p=0.007) controls. Additional qualitative results indicate widespread neuroinflammation present in local and remote white matter brain regions of both right and left IC stroke animals. With this model, we have successfully identified several downstream consequences of insular stroke. These findings provide insight into potential mechanisms of post-stroke AF, serving as future therapeutic targets for AFDAS.

1-C-53 Real-time evaluation of BACE1 activity on APP C99 site through a novel cell-based protein reporter

Bruno Herculano[1], Zhe Wang[1], Weihong Song[1]

[1]University of British Columbia

Current research on Alzheimer's Disease (AD) has at its core the generation of the Amyloid-beta peptide (Aβ) through the cleavage of the Aβ Precursor Protein (APP) by β-secretase (BACE1), though its specific regulatory factors are not yet completely understood. Currently available techniques for evaluating BACE1 rely on in vitro assays, limiting their usefulness. Here we describe a novel cell-based assay that mimics BACE1-mediated cleavage of APP, generating reporters that could be utilised for real-time assessment of BACE1 activity and screening of potential pharmacological treatments. We have generated a custom construct (ASGβ; Albumin-SEAP-eGFP-β site) expressing a chimera protein containing the β-site of APP and reporter signals. The alpha and gamma cleavage sites were removed to ensure specificity of the cleavage. Vectors encoding ASGβ and BACE1 were transfected into HEK cells, and selection was carried out through the use of Zeocin and Geneticin (G418) in order to generate a stable cell line. Co-expression with BACE1 demonstrably causes ASGβ to be cleaved at the expected BACE1 target site, generating an N-terminal fragment containing SEAP and eGFP as reporters that is subsequently released into the medium. This allows for real-time measurement of BACE1 activity through a phosphatase assay, with minimal disturbance to the cultured cells. Cleavage by BACE1 also generates a C-terminal fragment that can be easily observed through Western blot. Specificity was confirmed through the use of BACE1 inhibitor IV.

1-C-54 BACE2 is a conditional beta-secretase for Alzheimer Disease

Zhe Wang[1], Qin Xu[1], Fang Cai[1], Xi Liu[1], Weihong Song[1]

[1]University of British Columbia

Deposition of Amyloid β protein (Aβ) to form neuritic plaques is the characteristic neuropathology of Alzheimer's disease (AD). Aβ is generated from amyloid precursor protein (APP) by β- and γ-secretase cleavages. Enhanced β-cleavage of APP increases risk to develop AD. Beta-site APP cleaving enzyme 1(BACE1) is the β-secretase to cleave APP at the Asp1 site to

generate Aβ, and its homolog BACE2 prevents Aβ generation by cleaving APP at the θ-site (Phe20) within Aβ domain. Here we report that APP mutations that disrupt the juxtamembrane-helix (JH) of APP enabled BACE2 to cleave APP at the β-site both in vitro and in vivo. Furthermore, clusterin, a chaperone up-regulated during AD, bound APP to the JH, and induced BACE2-mediated β-cleavages of APP. Therefore, BACE2 may contribute to AD pathogenesis as a conditional β-secretase andcould be a preventive and therapeutic target of AD without the side effects of BACE1 inhibition.

1-C-55 A presenilin-1 mutation causes Alzheimer disease without affecting Notch signaling

Shuting Zhang[1], Yili Wu[1], Tahereh Bozorgmehr[1], Zhe Wang[1], Weihong Song[1]

[1]University of British Columbia

Presenilin-1 (PS1) is the catalytic subunit of the ã-secretase complex, and pathogenic mutations in presenilin-1 gene accounts for the majority cases of familial AD (FAD). FAD-associated mutant PS1 proteins have been shown to affect APP processing and Aâ generation and inhibit Notch cleavage and Notch signaling. In this report, we found that a novel PS1 mutation (Ser169del) alters APP processing and Aâ generation, and promotes neuritic plaque formation, and learning and memory deficits in AD model mice. However, this mutation did not affect Notch cleavage and Notch signaling in vitro and in vivo. Taken together, we demonstrate that PS1Ser169del has distinct effect on APP processing and Notch cleavage, suggesting that Notch signaling may not be critical for AD pathogenesis, and serine169 could be a critical site as a potential target for the development of novel ã-secretase modulators without affecting Notch cleavage to treat AD.

1-C-56 Inflammatory cytokines, klotho and DPP4 plasma levels in the patients with Alzheimer's disease

Mohsen Sedighi Mournani[1], Tourandokht Baluchnejadmojarad[1], Mehrdad Roghani[2], Siamak Afshin Majd[2]

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

Introduction Alzheimer's disease (AD) is the most common age-related and neurodegenerative disease characterized by the gradual process of memory loss and decline in cognitive function.

In this study, we measured the plasma levels of IL-1β, IL-6, TNF-α, klotho and DPP-4 in AD patients and compared them with healthy age-matched control. Material and methods 32 subjects were enrolled in the study and divided into two groups as AD (n =16) and healthy control (n=16). Diagnosis of the AD was done by the neurologist in the clinic and the using of the MMSE score. Plasma IL-1β, IL-6, TNF-α, klotho and DPP-4 levels were measured by ELISA in both groups and compared. Results Plasma levels of IL-1β and IL-6 were significantly higher in AD group than none AD, respectively (P = 0.006, P = 0.012). Data analysis showed a negative correlation between age and klotho levels in the AD group (R = - 0.56, P = 0.024). Meanwhile, there was a positive correlation between DPP4 levels and IL-1β (R = 0.62, P = 0.01) and TNF-α (R = 0.53, P = 0.03) in AD patients, respectively. Conclusion Il-1β and IL-6 are the parameters that significantly differed in the AD patients from healthy controls. Given the negative correlation between klotho and age in AD patients, low-level klotho may contribute to the pathogenesis of AD and neuroinflammation. Given that plasma DPP4 levels show a positive correlation with IL-1β and TNF-α, its level can be considered as a remarkable predictor of initiation and progress of inflammatory disease such as AD.

1-C-57 Protracted post-traumatic neuronal death in the developing hippocampus

Trevor Balena[1], Negah Rahmati[1], Yero Saponjian[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 earliest detectable events in the neurons post-trauma were an increase in caspase activity (as indicated by FLICA positivity), a reduction in the emission of virus-induced and transgenically-expressed fluorescent proteins (TurboRFP and Clomeleon, respectively), and an apparent retraction of all dendrites and axons. Next, neuronal membrane permeability progressively increased over several days and esterifed dyes such as SBFI-AM and Fura-AM permeated the cytosol. Cell membrane permeability to Na+ increased, which was associated with decreased membrane potential and increased cytoplasmic Na+ concentration. The terminal event was a sudden reduction in neuronal volume concurrent with engulfment by microglia. Mitochondrial potentials and Na+/K+ ATPase activity were

sustained throughout the process. Membrane permeability was reduced by cyclooxygenase (COX-2) inhibitors and Bax antagonists, but no intervention completely reversed the process. Overall, we describe here a new in vitro model of delayed neuronal cell death in the developing hippocampus.

1-C-58 Locomotor recovery following contusive spinal cord injury does not require oligodendrocyte remyelination

Sohrab Manesh[1], Greg Duncan[1], Brett Hilton[2], Peggy Assinck[3], Jie Liu[1], Aaron Moulson[1], Jason Plemel[4], Wolfram Tetzlaff[1]

[1]University of British Columbia, [2]Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), [3]The University of Edinburgh, [4]The University of Calgary

Remyelination occurs after spinal cord injury (SCI) but its functional relevance is unclear. We assessed the necessity of myelin regulatory factor (Myrf) in remyelination after contusive SCI by deleting the gene from platelet-derived growth factor receptor alpha positive (PDGFRα-positive) oligodendrocyte precursor cells (OPCs) in mice prior to SCI. While OPC proliferation and density were not altered by Myrf inducible knockout after SCI, the accumulation of new oligodendrocytes was prevented. This greatly inhibited myelin regeneration resulting in a 44% reduction in myelinated axons at the lesion epicenter. However, spontaneous locomotor recovery after SCI was not altered by remyelination failure. In controls with functional MYRF, locomotor recovery preceded the onset of substantial oligodendrocyte myelin regeneration. Collectively, these data demonstrate that MYRF expression in PDGFRα-positive cell derived oligodendrocytes is indispensable for oligodendrocyte myelin regeneration following contusive SCI but that remyelination is not required for spontaneous recovery of stepping.

1-C-59 A role for brain pericytes in cerebrovascular regeneration after stroke

Louis-Philippe Bernier[1], Jasmin Hefendehl[1], Coral-Ann Lewis[1], Wilder Scott[1], Lasse Dissing-Olesen[1], Fabio Rossi[1], Micheal Underhill[1], Brian MacVicar[1]

[1]University of British Columbia

Brain pericytes of the neurovascular unit are critical for the developmental maturation of cerebral blood vessels and for the integrity of the blood-brain barrier. Pericytes are perivascular

mural cells that share similarities with mesenchymal progenitors (MP), a cellular pool critical in supporting peripheral tissue regeneration. Therefore we examined what role brain pericytes play in repairing and restoring the cerebral microvasculature following stroke using a new transgenic MP reporter mouse that specifically identifies brain pericytes. Here we show that after stroke, pericytes enter the cell cycle to support cerebrovascular regeneration in a manner similar to their role during development. Following stroke, pericytes proliferate and migrate into the infarct region where they accumulate inside a border of reactive astrocytes. The pericyte-astrocyte interface forms an angiogenic zone that progressively migrates into the ischemic core, thereby supporting a wave of tissue revascularization. Within a few weeks normal vessels with an intact BBB are found perfusing the previously ischemic cortical area. Using single-cell and population RNA sequencing, we identify transcriptional signatures of naïve pericyte subpopulations as well as a functional and transcriptional profile of activated pericytes following trauma. Brain pericytes in the adult brain represent a major progenitor population that can modify their phenotype to contribute to the regeneration of cerebral blood vessels following injury in a process that recapitulates their role in developmental vasculogenesis.

1-C-60 Acute astrogliosis and behavioural deficits in rats following repeated mild traumatic brain injury

Melissa Clarkson[1], Brian Christie[1], Patrick Nahirney[1], Katie Neale[1], Sara Taylor[1]

[1]University of Victoria

Mild traumatic brain injury (mTBI), often referred to as concussion, has become increasingly recognized as a serious health issue in the general population. The prevalence of mTBI in athletes, particularly repeated injuries in young athletes, is of great concern as injuries to the developing brain can have long-term detrimental effects. Indeed, incurring repeated mTBI's (rmTBI) has been postulated to lead to conditions that include chronic traumatic encephalopathy (CTE). In this study we used a novel awake closed head injury (ACHI) model in rodents to examine rmTBI to determine if repeated injuries produced a progressive increase in astrogliosis in the brain, or if a there was a sudden increase that became apparent at some threshold. Animals were administered between up to 16 rmTBI's and acute neurological assessments were performed after each injury. We used Western blot analysis to quantify acute changes in glial fibrillary acidic protein (GFAP) to assess astrocytic activation, and also quantified levels of ionized calcium binding adaptor molecule 1 (IBA1) to examine microglia. We found each mTBI produced a reliable impact on the acute neurological assessment score, but that

significant increases in GFAP levels in the cortex and dentate gyrus of the hippocampus were only observed after 16 rmTBI's. These results help to clarify how rmTBI impacts inflammatory processes in the brain at a cellular level, and shows that behavioural deficits precede significant increases in astrogliosis.

1-C-61 Combining Visual Feedback and Functional Electrical Stimulation to Improve Motor Functions of Stroke Patients with a Brain-Computer Interface System

Slav Dimov[1], Christoph Guger[1], Rupert Ortner[2], Woosang Cho[2]

[1]g.tec neurotechnology USA, Inc., [2]g.tec medical engineering GmbH

A brain-computer interface (BCI) system can be used to detect motor intentions of stroke patients, and corresponding sensory feedback to the central nervous system can be used to reorganize the neural network because of neuroplasticity. In this study, the stroke patient is instructed to imagine either left or right wrist dorsiflexion, and a BCI system controls a forearm avatar in the monitor to provide visual feedback, while a functional electrical stimulation (FES) system producing a smooth passive dorsiflexion is triggered to provide tactile feedback. The linear discriminant analysis and a common spatial filter are applied to classify the recorded EEG data. There are 25 sessions over 13 weeks, including 240 trials of either left or right motor imagery. Four clinical measures were used two days before and after the training, including the upper extremity Fugl Meyer assessment (UE-FMA) to evaluate the motor impairment, modified Ashworth scale (MAS) to examine the spasm, Fahn tremor rating scale (FTRS) for the tremor, and Barthel index (BI) for daily activity. One male stroke patient (53 years old, 11 months post-stroke, right upper limb paralysis) participated this BCI training and quickly reached an average of maximal classification accuracy over 90% only after 5 sessions. The UE-FMA jumped from 25 to 46 points, suggesting behavioural improvement; MAS from 2 to 1, FTRS from 4 to 3, implying less spasticity and tremor, and BI increased from 90 to 95, meaning that he could be more independent in his daily activities.

1-C-62 Single APP knock-in mouse model of Alzheimer's disease showed age dependent cognitive deficit, cholinergic and catecholamine dysfunction

Sean Lacoursiere[1], Valerie Lapointe[1], Takashi Saito[2], Takaomi Saido[3], Bruce McNaughton[1], Robert Sutherland[1], Robert McDonald[1], Majid Mohajerani[1]

[1]University of Lethbridge, [2]RIKEN Brain Science Institute & Japan Science and Technology Agency, [3]RIKEN Brain Science Institute

Recently developed single APP knock-in mouse model (APPNL-G-F) for Alzheimer's disease (AD) has not been well characterized with respect to behavioral and neurochemical functions. The present study was designed to evaluate the age dependent memory functions and neurochemical alterations in the brain of this mouse model. Male C57BL/6 and APPNL-G-F mice were used in this study. Various behavioral tests (Morris water maze, fear conditioning, object recognition and balance beam) were performed at the age of 3, 6, 9 and 12 months. After behavioral tests, mice were perfused and immunostaining for cholinergic function (ChAT), tyrosine hydroxylase (TH), inflammatory markers and amyloid plaque was performed. At the age of 3 months the AD mice did not show any memory impairment. The AD mice at 6, 9, and 12 months of age showed impairment in memory functions as compared to age matched C57 mice in the water maze and fear test. At 9 and 12 months, the AD mice demonstrated an impairment of object associated memory compared to C57 mice. Results from the balance beam test showed no impairment of motor function at any age. The immunostaining results showed an increased amyloid plaque burden, neuroinflammation, and reduced number of ChAT positive cells in basal forebrain, TH positive cells in locus coeruleus of the AD mice's brain compared to C57 mice. These findings support the use of this novel mouse model to study AD pathology and to screen the treatment options for AD.

1-C-63 Extending the translational validity of the CHIMERA (Closed Head Impact Model of Engineered Rotational Acceleration) platform: defining the relationships between neurological, electrophysiological, biochemical and neuropathological outcomes

Asma Bashir[1], Sophie Stukas[1], Kurt McInnes[1], Zelalem Abebe[1], Igor Tatarnikov[1], Wai Hang Cheng[1], Carlos Barron[1], Anna Wilkinson[1], Guilaine Boyce[1], Matthew Farrer[1], Peter Cripton[1], Cheryl Wellington[1]

[1]University of British Columbia

CHIMERA (Closed Head Impact Model of Engineered Rotational Acceleration) is a recently described animal model of traumatic brain injury (TBI) that, at the mild level (0.7J), primarily produces diffuse axonal injury (DAI) characterized by white matter inflammation and axonal damage. CHIMERA was specifically designed to reliably generate a variety of TBI severities using precise and quantifiable biomechanical inputs in a non-surgical, user-friendly platform. The objective of this study was to define the upper limit of single impact murine moderate-severe

TBI (sTBI) with the use of a recently engineered an impactor interface that enables impacts up to 2.5J; we wished to define the relationship between biomechanical inputs and neurological, behavioral, electrophysiological, neuropathological and biochemical outcomes. Wild-type male and female mice aged 5-7 months were subjected to a single CHIMERA TBI at 2.5J; post-TBI outcomes were assessed at 6h and 2d time-points. We report that single sTBI using CHIMERA induces injury-dependent changes in behavioral and neurological deficits, grey matter microgliosis, and blood-brain barrier (BBB) extravasation. Intriguingly, we show tight positive correlations between TBI blood biomarkers of interest, namely tau protein, and increases in brain cytokine levels at 6h. Our data extend the validation of CHIMERA as a biofidelic animal model of head injury and establish working parameters to guide future investigations of the mechanisms underlying grey matter pathology and inflammation induced by mechanical trauma.

1-C-64 Effect Of Ischemia/Reperfusion Event On The Phosphorylation Of Mapk

Roxana Avalos-Chacon[1], Ricardo Santana-Martinez[1], Alma Ortiz-Plata[2], Perla Maldonado-Jimenez[2]

[1]Instituto Nacional De Neurología Y Neurocirugia, [2]Instituto Nacional De Neurologia Y Neurocirugia

Brain ischemia is the blocking of blood flow to the brain in which several mechanisms are activated, such as oxidative stress which is exacerbated during the restore of the normal blood flow event (reperfusion). It is known that the reactive species of oxygen to the activation of different signaling pathways; one of them is the MAPK pathway. The aim of the present work is to evaluate the effect of the ischemia/reperfusion event on the phosphorylation of the MAPK: JNK and p38 which have been associated to cell death in this kind of events. We work with an in vivo model of male Wistar rats that are exposed to 1 h of ischemia followed by short times of reperfusion and analyze the phosphorylation ratio of p38 and JNK in striatum, frontal cortex and hippocampus of rat brain using Western Blot. JNK was phosphorylated during the event of ischemia and this was maintained during the first 15 and 30 min after reperfusion in the striatum and hippocampus, while in the frontal cortex there were no changes. p38 was phosphorylated during the ischemia in the striatum and hippocampus, while in cortex there were no changes. After 15 and 30 min of reperfusion p38 was phosphorylated in striatum, cortex and hippocampus. It is shown that the MAPK associated with cell death are active during the event of ischemia reperfusion in different brain regions damaged with the MCAO model.

1-C-65 Ketogenic diet reduces inflammation after spinal cord injury

Kathleen Kolehmainen[1], Oscar Seira[1], Theresa Matzinger[2], Jie Liu[1], Wolfram Tetzlaff[1]

[1]University of British Columbia, [2]Franzens Universitat Innsbruck

Spinal cord injury (SCI) affects over 80 000 people in Canada and significantly impacts quality of life. Recent findings in our lab demonstrated that the ketogenic diet (KD) may be a promising SCI treatment as rats fed with KD acutely after cervical SCI showed behavioural improvement in forelimb function. KD is a high fat, low carbohydrate diet and is clinically used for drug-resistant epilepsy in children. We hypothesize that the beneficial effects of KD on recovery after acute SCI are in part due to modified inflammation. To assess inflammation after SCI we used a Meso Scale Discovery multiplex assay to determine the levels of pro-inflammatory and anti-inflammatory cytokines in Sprague-Dawley rats after cervical hemicontusion and in C57BL/6 mice after thoracic contusion. Interestingly we found that KD modulated cytokine production in the spinal cord of both species but by different mechanisms. In rats, KD rescued anti-inflammatory cytokine production (specifically Il-10) at 48 hours after injury. In mice, cytokine production did not differ between standard diet and KD at 48 hours post-injury but levels of MIP1alpha and MIP1beta, two pro-inflammatory cytokines involved in immune cell recruitment and activation, were reduced at 7 days post-injury on KD. Our results suggest that KD can reduce the inflammatory response in the injured spinal cord if administered beginning 4 hours after injury. Further research will look at the mechanism behind this modulation of cytokine production with an emphasis on macrophage subtypes present in the injured spinal cord.

1-C-66 Small molecule inducers of ABCA1 and apoE that act though indirect activation of the LXR pathway

Jianjia Fan[1], Rui Qi Zhao[1], Cameron Parro[1], Wenchen Zhao[1], Hsien-Ya Chou[1], Jerome Robert[1], Tarek Deeb[2], John Linley[3], Samantha Barichievy[3], Nicholas Brandon[3], Michael Wood[3], Iva Kulic[1], Cheryl Wellington[1]

[1]University of British Columbia, [2]Tufts-AstraZeneca Lab for Basic and Translational Neuroscience, [3]AstraZeneca

Apolipoprotein E (apoE) is the primary lipid carrier within the central nervous system (CNS) and the strongest genetic risk factor for late onset Alzheimer's disease (AD). We have previously shown that ATP-binding cassette transporter 1 (ABCA1) plays a critical role in lipidating CNS apoE. ABCA1 and apoE are both transcriptionally regulated by the liver X nuclear receptor (LXR) and evidence from genetic and pharmacological studies in AD mouse models suggests that increased levels of lipidated apoE can improve cognitive performance and can reduce amyloid burden in some strains. These findings support that pathways that increase ABCA1 and lipidated apoE are a potential therapeutic targets for AD. However, synthetic LXR agonists that are direct LXR ligands have undesirable side effects limiting their clinical use. Hence, there is interest in developing a new class of ABCA1 and apoE modulators with improved therapeutic potential. Here we describe small molecule antagonists of the purinergic receptor P2X7 that enhance ABCA1 expression and function and apoE secretion without being direct LXR ligands. This activity is only present in a subset of P2X7 antagonists. While these compounds were confirmed to block Bz-ATP-induced cell currents in P2X7 overexpressing HEK cells, the induction of ABCA1 and apoE occurs though a mechanism independent of P2X7. ABCA1 induction was consistently conserved across several CNS cell types. We have identified a novel dual activity compound that modulates ABCA1 though an indirect LXR mechanism and that independently inhibits P2X7.

1-C-67 Changes in Nrf2 nuclear translocation in cortex, striatum and hippocampus of rats, submitted to ischemia and reperfusion.

Cesar Gonzalez-Gutierrez[1], Ricardo Santana-Martinez[2], Alma Ortiz-Plata[1], Perla Maldonado-Jimenez[1]

[1]Instituto Nacional De Neurologia Y Neurocirugia, [2]Instituto Nacional De Neurología Y Neurocirugia

Cerebrovascular disease is a chronic-degenerative disorder that is divided into two types: ischemic (stroke) and hemorrhagic, whereas ischemic stroke being the third leading cause of death and permanent disability in adults worldwide. Reperfusion to ischemic brain is the best way to save life and limit the development of cerebral infarction. However, it is believed that ischemia-reperfusion injury (IR) is another important clinical problem in the treatment of brain damage. Evidence has shown that inflammation, ROS and apoptosis are mechanism involved in the cellular death. Therefore, it is reasonable for patients suffering from an IR event to benefit from reduced ROS levels in therapy in case of stroke. Nrf2 is considered one of the master regulators of endogenous antioxidant defense. In response to oxidative stress, Nrf2 promotes

the expression of a wide variety of antioxidant genes. Nrf2 appears to play an important role in the protection of brain cells against ischemic brain injury. The aim of this work was to evaluate the Nrf2 levels during ischemia with and without reperfusion. Animals were submitted to 5, 15, 30 and 60 min of ischemia and we established 60 min of ischemia and 15, 30, 60 and 120 min of reperfusion using the middle cerebral artery occlusion model, and the Nrf2 levels were measured by western blot in striatum, frontal cortex and hippocampus. Ischemia did not induce changes in protein levels of Nrf2 translocated to the nucleus in striatum nor cortex, however there is an increase in Nrf2 levels in rat hippocampus 30 min after lesion was established.

1-C-68 Assessing modulation of glutamate release in Huntington's Disease using iGluSnFR, an optogenetic probe

Ellen Koch[1], Cameron Woodard[1], Marja Sepers[1], Lynn Raymond[1]

[1]University of British Columbia

Aberrant glutamate transmission is associated with many neurological disorders, including Huntington's Disease (HD). HD is caused by a CAG repeat expansion in the huntingtin gene and results in substantial neurodegeneration, primarily in striatum and additionally in cortex and other regions. In a transgenic mouse model of HD, YAC128, cortical-striatal glutamate release was shown to be increased at 1 month of age and decreased at 12 months, and NMDA receptor signalling is altered in HD. However, little is known about alterations in modulation of cortical glutamate release onto striatal neurons in HD. The iGluSnFR is an optogenetic probe that can be used to image glutamate dynamics in real-time. We exposed acute cortical-striatal brain slices to pharmacological and physiological manipulations expected to decrease cortical glutamate release onto striatal neurons. Activation of presynaptic Group II mGluRs, GABAB, and CB1 receptors, as well as low calcium conditions all resulted in a decrease in evoked iGluSnFR responses, reflecting the expected inhibition of glutamate release. Now we are using iGluSnFR to investigate whether other presynaptic elements are affected in HD, such as calcium channels, NMDA and dopamine receptors, and determine the contribution of altered glutamate release to cortical-striatal synaptic plasticity induced by tetanic stimulation protocols. Our experiments validate iGluSnFR as an accurate tool to study modulation of glutamate release in brain slice, and future work will allow us to directly study mechanisms of glutamate transmission in HD.

1-C-69 Dietary Fats Modulate Select Immune Functions of Microglia

Jessica Lowry[1], Andis Klegeris[1]

[1]University of British Columbia Okanagan

Alzheimer's disease (AD) is the most common cause of dementia. While no effective treatment currently exists for AD, several significant AD risk factors are preventable, including obesity, hypertension and dietary factors. Polyunsaturated fats have been shown to modulate peripheral and central nervous system (CNS) inflammation. Microglia regulate the immune responses of the CNS, and their adverse activation has been observed in AD. We hypothesized that dietary fats can regulate microglial immune functions, which could be a mechanism linking polyunsaturated fat intake with CNS immunomodulating effects. Mouse BV-2 microglia were treated with alpha-linolenic acid (ALA) or linoleic acid (LA) for 24h, followed by pro-inflammatory stimulation with bacterial lipopolysaccharide (LPS) for 24h. BV-2 microglia supernatants and proteins were collected. The supernatants were used to quantify the secretion of reactive nitrogen species (RNS) by BV-2 cells. Proteins were used to quantify inducible nitric oxide synthase (iNOS) by immunoblotting. Both ALA and LA significantly reduced RNS secretion by LPS-stimulated BV-2 microglia. LA, but not ALA, significantly reduced iNOS levels in LPS-stimulated microglia. Microglial phagocytosis, release of reactive oxygen species and monocyte-chemoattractant protein were not affected by ALA or LA. Dietary fatty acids can modulate select microglial immune responses, and should be further investigated for their roles in CNS inflammation, which can contribute to the progression of AD.

1-C-70 Death-associated protein kinase 1 promotes extrasynaptic GluN2B phosphorylation and striatal spine loss in Huntington disease

Mandi Schmidt[1], Louisa Dal Cengio[1], Nicholas Caron[1], Nikola Lazic[1], Lynn Raymond[1], Michael Hayden[1]

[1]University of British Columbia

Huntington disease (HD) is a devastating neurodegenerative disorder caused by a CAG repeat expansion in the huntingtin (HTT) gene. HD is characterized by motor, psychiatric, and cognitive disturbances resulting from cortico-striatal synaptic dysfunction and degeneration of striatal medium spiny neurons (MSNs). In multiple HD mouse models including the YAC128 transgenic model expressing human mutant HTT, one of the earliest synaptic alterations to occur is enhanced striatal extrasynaptic (ex) N-methyl-D-aspartate receptor (NMDAR) expression and

activity. This activity is mediated primarily through GluN2B subunit-containing receptors and is associated with increased activation of cell death pathways, inhibition of survival signaling, and greater susceptibility to excitotoxicity in YAC128 MSNs. Death-associated protein kinase 1 (DAPK1) is a pro-apoptotic calcium/calmodulin-regulated kinase highly expressed in neurons during development. Under excitotoxic or ischemic conditions in the mature brain, DAPK1 becomes re-activated and recruited to exNMDAR complexes where it phosphorylates GluN2B at S1303, amplifying receptor function. Genetic and pharmacological approaches designed to reduce DAPK1 activity have demonstrated benefit in animal models of stroke and Alzheimer disease, indicating that DAPK1 may be a novel therapeutic target for neuroprotection. In the present study, we establish that DAPK1 contributes to mutant HTT-induced dysregulation of GluN2B receptors, and demonstrate that DAPK1 inhibition may be a novel strategy to preserve synaptic function in HD.

1-C-71 1. Functional Biomarkers of Parkinson's disease: Changes in brain-wide network connectivity in Default Mode and Frontal-parietal Control Networks

Nole Hiebert[1], Lorina Naci[2], Adrian Owen[1], Penny MacDonald[3]

[1]Brain and Mind Institute/ Western University, [2]Trinity College Dublin, [3]Western University

Parkinson's disease (PD) is a progressive, neurological disorder for which there are no reliable biomarkers. The aim of this study was to investigate the potential of functional biomarkers to distinguish between PD patients and controls as well as to track PD progression. 15 patients with PD and 10 matched healthy controls were tested on two separate occasions, once on and in another session off dopaminergic medication. Participants watched a different short film clip in each session, while brain activity was simultaneously acquired using 3T fMRI. These naturalistic stimuli are known to activate distinct neural networks in a specific and reproducible manner among healthy controls. Network time courses from a group of young, healthy controls provided the standard for high-level cognitive (i.e., default mode and fronto-parietal control) and low-level perceptual (i.e., visual and auditory) networks to which PD patients and healthy age-matched controls were compared. Deviations in the synchronization within each of these neural networks provided an innovative means to capture deficits in sensory and cognitive processing to serve as functional biomarkers of disease. Synchronicity was measured by the number of activated voxels within each network that positively correlate with the timecourses from the young, healthy dataset. Synchronization within the fronto-parietal control network (FPCN)—the network tracking highest level of information and expected to be first-affected in

PD due to its reciprocal connection to dorsal parts of the striatum—was significantly greater in he

1-C-72 Biomarkers in amyotrophic lateral sclerosis: a metallomics approach

Deise Mendonça[1], Jessica Paloma Silva[1], Renata Barbosa[2], Edgar Francisco de Jesus[3], Leila Chimelli[4], Ana Maria Martinez[3]

[1]Federal University of Sergipe, [2]São Paulo University, [3]Federal University of Rio de Janeiro, [4]Paulo Niemyer State Institute of the Brain

Amyotrophic Lateral Sclerosis (ALS) is the most common motor neuron disease in adults but its etiology remains unknown. Biological samples analysis provides a powerful strategy to investigate pathological processes and studies indicate a role of trace metals in ALS. In this work we aimed to investigate the levels of trace metals in ALS CSF samples. CSF samples from ALS cases (10) and control cases (6) were analyzed by X-ray Microfluorescence with Synchrotron Radiation. The measurements were performed on the XRF beam line at the National Synchrotron Light Laboratory (Brazil). Each element intensity spectrum was obtained with AXIL software (distributed by the International Atomic Energy Agency). Data obtained were statistically analyzed by General Linear Models, in a multivariate based analysis method. The following elements were analyzed: aluminum, bromine, calcium, chlorine, copper, chromium, iron, potassium, phosphorus, nickel, rubidium, silicon, sulfur and zinc. In ALS CSF samples, a significant increase of calcium, chlorine and potassium concentration was observed compared to control samples. Excitotoxicity is one of the many factors implicated in the pathogenic process of ALS. The intracellular calcium influx appears to contribute to neurodegeneration in multiple pathways, leading to cell death. Activation of potassium and chlorine channels by increased calcium level has been described and prolonged outflow of both may be involved with apoptosis. Elevated CSF levels of these three elements indicate a possible molecular pathway involved in disease pathogenic process.

1-C-73 Microglial maturation, dysfunction, and role in synaptic loss in Huntington's disease

Julie Savage[1], Marie-Kim St.-Pierre[1], Hassan El-Hajj[1], Maria Sanchez[1], Francesca Cicchetti[1], Marie-Eve Tremblay[2]

[1]Université Laval, [2]Centre de recherche du CHU de Québec

Huntington's disease (HD) is a dominantly inherited progressive disorder that affects a person's cognitive and motor abilities. HD is caused by excess CAG repeats within the Huntingtin gene which cause HTT protein to be misfolded and form aggregates within neurons. We studied the maturation and dysfunction of microglia, the brain's resident macrophages, within the R6/2 model of HD. R6/2 mice display progressive motor deficits beginning at 6 weeks, and are incapacitated by 13 weeks. We studied microglial morphology, phagocytic capacity, and synaptic contacts and verified synaptic loss in the striatum of R6/2 vs wild-type littermates. At 3 weeks of age, prior to motor deficits or synaptic loss, microglia in R6/2 animals have a smaller morphological index, consistent with a mature phenotype. By 10 weeks of age, microglia from R6/2 mice demonstrate increased phagocytosis as analyzed by light microscopy and immunoEM. Ultrastructural analysis also revealed microglial cell bodies from 3 or 10-week old R6/2 animals were more likely to perform extracellular degradation and contain phagocytic material than control. Furthermore, microglial processes in 10-week old R6/2 mice were less likely to make contact with synaptic elements, while processes in 3-week old R6/2 mice were more likely to contact synapses. We also performed 3D FIB-SEM analysis and dendritic reconstructions to study the pattern of progressive synaptic loss in the R6/2 striatum. These data indicate that microglia play an intimate role in HD pathogenesis and may be a target for therapeutic intervention.

1-C-74 Canonical Wnt Pathway is Required for Maintenance of the Blood Brain Barrier Integrity Upon Stroke: Impact on Thrombolytic Therapy

Noëmie Jean LeBlanc[1]

[1]CHUL

Stroke triggers blood brain barrier (BBB) disruption. Administration of tissue plasminogen activator (tPA) within a therapeutic window of 4.5 hours after onset constitutes the only existing treatment. Beyond this window, tPA worsens BBB disruption and causes hemorrhagic transformation. Canonical Wnt pathway induces BBB formation during ontogeny. Evidence suggests that the pathway is required to maintain BBB integrity after ischemic stroke. We hypothesize here that pathway activation might constitute a promising approach to improve tPA therapy via protection of the BBB. For this purpose, male C57BL/6 mice were subjected to focal cerebral ischemia and treated with tPA 6h post-stroke with or without 6-BIO, an activator of the canonical Wnt pathway. In parallel, murine cerebral endothelial cells (bEnd3) exposed to oxygen

and glucose deprivation (OGD) were used to dissect the underlying mechanisms. Our data demonstrate that tPA delayed administration exacerbates immunoglobulin G (IgG) extravasation into the brain and causes intracerebral bleeding. 6-BIO attenuates these detrimental effects without influencing histological injury and inflammation, indicating that the effects of systemic 6-BIO administration are mainly vascular. Cell-based assays show that tPA does not influence pathway activity per se, and that OGD induces expression of plasmalemmal vesicle-associated protein (PLVAP) that is involved in endothelial permeability. These results demonstrate that activation of the canonical Wnt pathway improves tPA therapy via promotion of BBB integrity.

1-C-75 Neuropathies of Stüve-Wiedemann Syndrome due to mutations in leukemia inhibitory factor receptor (LIFR) gene

Alexandra Oxford[1], Cheryl Jorcyk[1], Julia Oxford[1]

[1]Boise State University

Stuve-Wiedemann syndrome (STWS; OMIM #610559) is a rare disease that results in dysfunction of the autonomic nervous system, which controls involuntary processes such as breathing rate and body temperature. In infants, this can result in respiratory distress, feeding and swallowing difficulties, and hyperthermic episodes. Individuals may sweat excessively when body temperature is not elevated. Additionally, individuals have reduced ability to feel pain and may lose reflexes such as the corneal reflex that normally causes one to blink, and the patellar reflex resulting in the knee-jerk. STWS usually results in infant mortality, yet some STWS patients survive into early adulthood. STWS is caused by a mutation in the leukemia inhibitory factor receptor (LIFR) gene, which is inherited in an autosomal-recessive pattern. Most LIFR mutations resulting in STWS cause instability of the mRNA due to frameshift mutations leading to premature stop codons, which prevent the formation of LIFR protein. STWS is managed on a symptomatic basis as no treatment is currently available.

1-C-76 Altered endocannabinoid-mediated excitatory synaptic plasticity in the striatum in a Huntington disease mouse model

Marja Sepers[1], James Mackay[1], Matthew Hill[2], Lynn Raymond[1]

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

Huntington disease (HD) pathogenesis includes a loss of neurons most notably in the striatum. Altered glutamate signaling is evident in animal models of HD and may contribute to the selective vulnerability of striatal projection neurons (SPN). However, it was previously unknown if excitatory synapses in the HD striatum could by modulated by synaptic plasticity. We have recently shown by recording in acute brain slices that long-term depression (LTD) mediated by the endocannabinoid anandamide is impaired in YAC128 HD mice at cortico-striatal synapses. Interestingly, the impairment is not due to a reduction in the expression or signaling of the presynaptic cannabinoid receptor 1 (CB1). Plasticity mediated by the endocannabinoid 2-AG is also unchanged in YAC128 suggesting that the impairment in LTD is due to deficient production of anandamide in SPN. Notably, anandamide synthesis depends on L-type voltage-gated Ca2+ channels (L-VGCC) and Ryanodine receptor-mediated Ca2+-induced Ca2+ release, both of which may be altered early in HD. We have found changes in Cav1.2 and Cav1.3 L-VGCC function in SPN of YAC128 mice compared to wild-type littermates, and have also measured the basal levels of anandamide and 2AG. Further experiments will investigate the impact mutant huntingtin on Ryanodine receptor-mediated intracellular Ca2+ release. These findings will increase our understanding of early deficits in motor learning and striatal vulnerability in HD.

1-C-77 Effect of lactate or medium chain triglycerides on behaviour and blood lactate and glucose.

Michael Murack[1], Hazim Khalil[1], Claude Messier[1]

[1]University of Ottawa

In an early attempt to understand the mechanisms of electroconvulsive therapy's (ECT) effect on depressive symptoms, Lowenbach et al. (1947) observed that the daily administration of a lactate/lactic acid beverage reduced symptoms and improved sleep in about 55% of a small group of institutionalized patients. However side effects included cramps, nausea, and poor palatability. Ketones, known moderators of peripheral blood lactate, may prove a viable alternative to the lactate/lactic acid solution used by Lowenbach. CD-1 mice were individually gavaged for three days with a single dose of lactate/lactic acid mix (0.59g/kg, 0.47g/kg,0.35g/kg,0.24g/kg or 0.12g/kg) or a Medium Chain Triglyceride (MCT) oil made up of capric/caprylic acid (10mL/kg, 5mL/kg, 2.5mL/kg or 1mL/kg) after 2 hours fasting. Lactate and glucose concentrations were analyzed from peripheral blood collected 30 mins pre-administration and each consecutive 30 mins for 3 hours. MCT oil (10mL/kg) significantly increased blood lactate concentration for 2 hours and 5mL/kg for 30 mins compared to control.

Mice administered 0.47g/kg lactate/lactic acid mix had significantly greater blood lactate concentration than the lower dosses and control by the third day. However, the higher doses of MCT reduced weight and also decreased blood glucose contractions. Finally, the repeated administration of high doses of lactate or MCT led to increased sleep. The results suggest that increasing blood lactate could improve sleep and support the early Lowenbach observations.

1-C-78 Effects of Ketogenic diet in mitochondrial function after Spinal Cord Injury

Oscar Seira[1], Kathleen Kolehmainen[1], Jie Liu[1], Robert Boushel[2], Wolfram Tetzlaff[1]

[1]University of British Columbia, [2]University of British Columbia (University of British Columbia)/ICORD

Spinal Cord Injury (SCI) pathophysiology can be attributed to either primary physical injury, or the delayed, secondary injury cascades which begin after the initial injury and can persist for several months. A better understanding of the secondary injury mechanisms is essential in developing potential therapies to prevent damage, increase neuroprotection, restore metabolic deficits and finally promote functional recovery following SCI. Indeed, previous studies have shown that dysregulated metabolism and energetic deficits linked to mitochondrial bioenergetics deficiencies are severely affected after SCI. We found that metabolism of ketones after SCI in rats has neuroprotective and improved behavioural effects. We hypothesized that a high fat, low carbohydrate ketogenic diet (KD) will improve mitochondrial function after SCI. Using a C5 hemi-contusion model in adult male rats we examined the states of mitochondrial respiration and assessed the different components of the electron transport system (ETS). Starting 4 hours following the injury, animals were fed either a standard control diet (SD) or KD. As expected, mitochondrial function was reduced after SCI. However, administration of KD increased the expression of PGC1-α, a major regulator of mitochondrial biogenesis, and partially rescued function of Complexes I,II and protein expression of Complexes I, II, and III at 7 days after SCI. Results from the present study suggest that the use of KD may improve post-SCI metabolism by rescuing mitochondrial dysfunction, and might be a beneficial treatment for acute SCI.

1-C-79 MicroRNA Biomarkers for Injury Severity in Acute Human Traumatic Spinal Cord Injury

Seth Tigchelaar[1], Rishab Gupta[1], Femke Streijger[2], Sunita Sinha[3], Stephane Flibotte[3], Michael Rizzuto[1], Kendall Van Keuren - Jensen[4], Corey Nislow[3], Brian Kwon[2]

[1]ICORD, [2]University of British Columbia, [3]Pharmaceutical Sciences, [4]Translational Genomics

Introduction: With limited treatment options currently available to clinicians, there is an urgent need for non-invasive biomarkers to aid in the scientific development and clinical validation of novel therapies for acute spinal cord injury (SCI). MicroRNAs are small regulatory noncoding RNA molecules that mediate gene expression. The current body of literature suggests that microRNAs orchestrate a wide range of biological processes such as inflammation, synaptic plasticity and apoptosis. Many microRNAs are highly enriched in the nervous system and are also directly implicated in the pathogenesis of various neurodegenerative diseases including traumatic brain injury and SCI. Methods: In this study, we compared the cell-free expression profiles of microRNA in serum and cerebrospinal fluid (CSF) collected from human patients with SCI. Patients classified as AIS A, B, or C were recruited as part of an ongoing, multi-center study called CAMPER. CSF and blood samples were collected every 8 hours for 5 days in order to compare CSF and serum microRNA profiles following injury. Next generation sequencing was used to compare the effects of injury severity on microRNA levels. Results: Here, we present microRNA profiles in CSF and seurm clinical samples during acute stages of SCI. This analysis was done in parallel to the investigation of microRNA in the serum of pigs following SCI. This characterization is important to establish whether biomarkers of SCI found in pigs can be transferred to humans and vice-versa.

1-C-80 Longitudinal Assessment of Behavior in a Novel Progressive Model of Parkinson's Disease

Logan Bigelow[1], Melissa Perry[1], Jackalina VanKampen[1], Andrew Tasker[1]

[1]University of Prince Edward Island

Chronic consumption of beta-sitosterol-d-glucoside (BSSG), a component of the cycad seed, by rats initiates a progressive pathology that develops over several months following treatment. The motor, non-motor and associated underlying histopathological alterations that emerge following this feeding regiment resemble those seen in Parkinson's Disease (Van Kampen et al. 2015). As part of a multi-site validation study, we are replicating and further characterizing the BSSG model, with a particular focus on vulnerable cognitive processes in PD Beginning at 3 months of age, male CD rats were fed either a flour pellet or a flour pellet laced with BSSG (3mg)

5x/week for 16 weeks. Following BSSG intoxication, animals were exposed to a behavioural test battery at 16-, 24-, 32-, or 40-weeks post initial BSSG feeding (n=10 per group). The battery included open field, novel object recognition task, spontaneous alternation, and attentional set-shifting. Following behavioural assessment, all animals are transcardially perfused and their brains removed for assessment of relevant molecular biomarkers of PD by immuno-histochemistry. Behavioural analysis completed to date of the 16- and 24-week time points indicates no differences in all measures. The absence of any group differences at the early assessment points may be indicative of a pathology that has not progressed sufficiently to induce deviations from normal behaviour. These early time points may correspond to the prodromal period of PD development. Supported by the Weston Brain Institute

1-C-81 Acute cellular response of the neurovascular unit following a small focal ischemic stroke.

Kathleen Fifield[1], Jacqueline Vanderluit[1]

[1]Memorial University of Newfoundland

Introduction Ischemic stroke is a debilitating neurovascular disease that occurs following occlusion of blood vessels within the brain. Reduction in cerebral blood flow causes immediate cell death within the ischemic core whereas in the hypo-perfused tissue surrounding the core cells are viable but susceptible to further injury. In the acute period following stroke cells have the greatest potential for rescue. Cell-cell interactions within the neurovascular unit (NVU) maintain cell survival and homeostasis. Here, we examined the timing of cellular responses of the NVU to an acute ischemic stroke. Methods Focal ischemic stroke was induced with an intra-cortical injection of the vasoconstrictive peptide Endothelin-1 (ET-1) and saline was used as a control injury. Dextran-conjugated Texas Red was administered to identify perfused regions around the infarct. The cellular response within the NVU was examined at acute time points post-stroke. Results In the hypo-perfused area surrounding the infarct, astrogliosis was observed as early as 4 hours post-stroke and neuronal cell death occurred within the first 8 hours of stroke and remained stable up to 72 hours. Blood brain barrier breakdown was observed at 24 hours and coincided with an increase in neuroinflammation. Conclusion Breakdown of cell-cell communication within the NVU affects the health of astrocytes and neurons in the early hours post-stroke. Elucidating the cellular response within the NVU and identifying techniques to maintain cellular communication surrounding the infarct may be a potential therapeutic strategy.

1-C-82 Probing neural correlates of spatial navigation deficits in a second generation mouse model of Alzheimer's disease (APPNL-G-F)

Samsoon Inayat[1], Jogender Mehla[1], Jianjun Sun[1], Jaira Ranger[1], Robert Sutherland[1], Bruce McNaughton[1], Majid Mohajerani[1]

[1]University of Lethbridge

One of the earliest symptoms in Alzheimer's disease (AD) patients is spatial disorientation corresponding to amyloid beta (Aβ) pathology in brain. Using a 2nd generation AD mouse model APPNL-G-F, we are investigating changes at the neuronal level that accompany the development of spatial disorientation. In the Morris water maze task, AD mice showed deficits in spatial navigation starting at the age of 6 months following the onset of Aβ pathology at 3 months of age. We theorize that Aβ plaques adversely affect neural circuits leading to impairments in responses of neurons encoding spatial information such as place cells. We hypothesize compromised place cells in the CA1 region of the hippocampus and the retrosplenial cortex in 6 months old AD mice compared to controls and the progression of impairment correlated with an increase in Aβ plaques. To this end we have devised a novel behavioral paradigm to identify place cells in head-restrained mice using two photon calcium imaging with GCaMP6 viral vectors. In our behavioral paradigm which requires little training, a mouse is forced to run on a treadmill away from an aversive stimulus, a mild air puff, and has to cover a fixed distance before reaching a safe place with no air puff. Using a cue less belt, we have identified path-integration cells while with tactile, auditory, and visual cues on the belt, we can find place cells. Next we will compare the population of place cells and properties of place fields in AD mice versus controls. We will also study if impaired place cells lie in the vicinity of Aβ plaques.

1-C-83 Aberrant ER Ca2+ handling alters synaptic glutamate release in the YAC128 mouse Huntington Disease Model

James Mackay[1], Amy Smith-Dijak[1], Ellen Koch[1], Lynn Raymond[1]

[1]University of British Columbia

Huntington disease (HD) is a hereditary neurodegenerative disorder caused by a CAG repeat expansion in the huntingtin (HTT) gene and characterized by relatively selective striatal spiny projection neuron (SPN) degeneration. Although the mechanisms of mutant HTT (mHTT) neurotoxicity are not fully understood, enhanced extrasynaptic NMDA-type glutamate receptor expression appears to play a role, as does a persistent mHTT-mediated ER Ca2+ leak. Glutamate release onto striatal SPNs from cortical terminals is also altered in HD, potentially compounding excitotoxicity; however, conflicting reports show both enhanced and reduced cortical glutamate release in HD models. Here we show that glutamatergic mini excitatory postsynaptic currents (EPSC) are more frequent in pyramidal neurons from YAC128 mouse-derived cortical cultures. Since ER stores can release Ca2+ to elevate transmitter release, we hypothesized that a presynaptic ER Ca2+ leak underlies EPSC frequency enhancement. Consistent with this, releasing ER Ca2+ with caffeine or low-dose ryanodine (5M) elevated EPSC frequencies in wildtype (WT) but not YAC128 cultures. Furthermore, depleting ER stores with cyclopiazionic acid and removing extracellular Ca2+ reduced EPSC frequencies in YAC128 but not WT cultures. Notably, cortical neuron YAC128 EPSC frequencies were significantly lower than WT in the presence of CPA and 0 Ca2+, suggesting that YAC128 neurons have fewer excitatory synapses. Structural synapse measurements are underway to investigate this, as are Ca2+ imaging experiments to directly measure presynaptic Ca2+ levels.

1-C-84 Timing of acute vasopressor administration after traumatic SCI: The impact on blood flow, oxygenation, pressure, and metabolic responses using a porcine model

Amanda Cheung[1], Kitty So[1], Femke Streijger[1], Elena Okon[1], Neda Manouchehri[1], Katelyn Shortt[1], Sheung Man Keung[1], Kyoung-Tae Kim[1], Allan Fong[1], Jenny Sun[1], Donald Griesdale[1], Mypinder Sekhon[1], Brian Kwon[1]

[1]University of British Columbia

There are currently limited early intervention strategies for patients who suffer acute spinal cord injury (SCI). Vasopressor support of mean arterial blood pressure (MAP) to improve spinal cord blood flow is one of the few treatment options available. However, the effect of intervention timing, on blood flow, oxygenation, and metabolic responses warrants consideration. The focus of this study is to determine the timing and effect of MAP support intervention on acute hemodynamic and metabolic responses during the compressed and decompressed states of injury. Using our porcine model of SCI, a T10 contusion injury was administered followed by 2-hours of sustained compression. After SCI, norepinephrine was used to elevate MAP by 20

mmHg for a period of 1.5 to 3.0 hours while the cord was compressed, after the cord was decompressed, or during both injury states. Laser Doppler flowmetry/oxygenation, fibre optic pressure, and microdialysis probes were used to measure spinal cord blood flow (SCBF), oxygenation (PO2), and spinal cord pressure (SCP). Microdialysis samples were collected to analyze for lactate, pyruvate, glucose, glutamate, and glycerol. Our data suggests that MAP augmentation during compression or decompression of the spinal cord modestly restores SCBF and PO2 and reduces the lactate/pyruvate ratio more effectively during compression. However, MAP augmentation during both states of injury may result in deleterious effects due to increased total hemorrhage observed near the injury site.

1-C-85 Noradrenergic fiber degeneration in the piriform cortex and a difficult odor pattern separation deficit are observed in an Alzheimer's disease model mimicking Braak's pretangle hyperphosphorylated tau in the locus coeruleus

Abhinaba Ghosh[1], Bandhan Mukherjee[1], Faith McCarthy[1], Vanessa Strong[1], Susan Walling[1], Gerard Martin[1], Carolyn Harley[1], Qi Yuan[1]

[1]Memorial University Of Newfoundland

Human studies now reveal the presence of hyperphosphorylated tau in the locus coeruleus (LC), a pontine noradrenergic hub, as the first 'pretangle' signature of Alzheimer's Disease (AD). AD-related cognitive loss has been shown to correlate inversely with LC neuron number. LC cell loss occurs in mid to late, but not early, AD. We hypothesize that noradrenergic axonal degeneration may occur during pretangle or early AD stages and be indexed by impairments in difficult pattern separation, a task known to be modulated by LC input in rats and humans. We developed a rat LC AD model by transfecting LC neurons in TH-CRE rats using infusion of an AAV viral vector containing the human tau gene pseudophosphorylated on 14 sites (AAV2/9-rEF1a-DIO-eGFP-htauE14-WPRE) known to be hyperphosphorylated in human LC. GFP only AAV is used as a control. In rats infused at 2 months and tested 7 months later, htauE14-expressing rats were impaired in acquiring a highly similar odor discrimination compared to controls. Both groups were successful with a dissimilar odor discrimination problem. Immunohistochemistry using dopamine-β-hydroxylase and norepinephrine transporter antibodies demonstrated significant loss of noradrenergic fibers in the olfactory piriform cortex in htauE14 rats. There was no neuron loss in LC. These results parallel findings of decreased NE fibers in human AD and suggest cognitive tests requiring difficult pattern separations may index early LC dysfunction and provide an early probe for the success of AD therapies.

1-C-86 When the garbage truck malfunctions: Glymphatic clearance visualization following repetitive TBI in adolescent female rats

Jennaya Christensen[1], Glenn Yamakawa[1], David Wright[2], Sandy Shultz[2], Richelle Mychasiuk[1]

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

Traumatic Brain Injury (TBI) is one of the most common, yet neglected, pediatric health issues in North America. Individuals who experience repetitive mild TBI (RmTBI) generally exhibit poorer developmental outcomes. Possible causes for the poor neurological outcomes associated with RmTBI may include neuroanatomical modifications or deficient removal of injury-induced waste. The glymphatic system is a brain-wide paravascular pathway that is responsible for the clearance of macroscopic waste from the CNS. This waste removal system is more active during sleep and radically inhibited during wakefulness. Since sleep disturbances are regularly reported following a TBI, the glymphatic system seems to be a promising candidate in explaining the development of post-concussive syndrome (PCS). Therefore, we induced 3 mild traumatic brain injuries (mTBI) in adolescent female rats prior to volumetric and diffusion magnetic resonance imaging (MRI). During the MRI procedure, an injection of gadolinium, a paramagnetic contrast agent, was situated within the cisterna magna to allow for visualization and assessment of glymphatic system function. A behavioural test battery, including time-to-right, beamwalk, and elevated plus maze, was used to assess symptomology consistent with PCS. RmTBI produced behavioural impairments that mimic PCS in patient populations. Glymphatic system assessment MRI scanning is complete with statistical analysis currently underway. Understanding the role of the glymphatic system in the pathophysiology of RmTBI may permit targeted therapeutics and improve recovery.

1-C-87 The differential effects of ketamine, Ro25-6981 and (2R, 6R)-HNK on synaptic plasticity and depressive-like behaviour in the Wistar-Kyoto rat

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

[1]University of British Columbia

Accumulating evidence implicates dysfunction within the glutamatergic system, dysregulation of synaptic plasticity and neuronal atrophy, particularly in the hippocampus (HPC), in the

pathophysiology of depression. The effects of ketamine on synaptic plasticity in animal models of depression, as well as their direct contribution to ketamine's antidepressant effects, are still unclear. Here we utilized Wistar-Kyoto (WKY) rats, a stress-prone strain with behavioural, neurochemical and endocrine parallels to clinical depression, and found that WKYs have impaired hippocampal CA1 long-term potentiation (LTP) in vivo. Importantly, a single injection of ketamine, which produced significant rapid and sustained antidepressant effects in WKYs, also acutely restored the impaired CA1 LTP and led to a subsequent increase in basal CA1 transmission, as well as an upregulation of AMPAR subunit surface expression in the HPC at 24h after ketamine administration. In contrast, the NR2B-specific NMDAR antagonist Ro25-6981, which unlike ketamine only transiently reduced depressive behaviours, failed to restore hippocampal LTP in WKYs. The active ketamine metabolite (2R,6R)-hydroxynorketamine (HNK) mimicked ketamine's synaptic effects by rescuing LTP, but seemed to lack keteamine's antidepressant action. We conclude that ketamine's effects on synaptic plasticity and AMPAR function may contribute to its mechanism of action as an antidepressant by leading to synaptic strengthening and synaptogenesis, thus counteracting the reduced synaptic drive in corticolimbic brain regions seen in depression.

1-C-88 Behavioural and Pathophysiological Effects of Sleep Deprivation Following Repetitive Mild Traumatic Brain Injury in Adolescent Rats

Sabrina Salberg[1], Jennaya Christensen[1], Glenn Yamakawa[1], Haris Malik[1], Jason Tabor[1], Ali Hazari[1], Richelle Mychasiuk[1]

[1]University of Calgary

A strongly held dogma maintains that one should be kept awake after a mild traumatic brain injury (mTBI) to prevent a coma. This however conflicts with the known benefits of sleep: repair and restoration. We therefore sought to examine the effects of sleep deprivation (SD) in the post-traumatic sleep period on post-concussion symptomology (PCS). Adolescent male (n=22) and female (n=24) rats were administered repetitive mTBIs (RmTBI) or sham injuries and were then assigned to 5hrs of SD or left undisturbed. All animals were then tested using seven behavioural tasks previously validated in our laboratory to examine PCS; time-to-right (loss of consciousness), beam walking (balance and motor control), open field (exploratory behaviour), elevated plus maze (anxiety), novel context mismatch (short-term memory), von frey (pain tolerance), and force swim (depression). This was followed by analysis of serum cytokines, and qPCR for mRNA expression. Exposure to 3 SD epochs significantly impaired behaviour in 4/7 of

the measures for both sham and RmTBI animals, while RmTBI also produced dysfunction in 5/7 tests, but the effects of SD and RmTBI were not cumulative. SD induced long-lasting changes in serum levels of Tnf-α, IL6, and IL-1ß. mRNA expression in the prefrontal cortex, hippocampus, hypothalamus, and anterior cingulate was modified in response to SD and RmTBI, but similar to the behavioural measures, the mRNA changes were not cumulative. However, given that SD often produced impairments similar or worse than RmTBI, sleep hygiene should become a priority for adolescent health.

1-C-89 The human TOR1A gene is a novel GSK3beta target gene

Ioanna Armata[1], Sandra Turcotte[1]

[1]The University of Moncton

Early Onset Dystonia (EOD) represents one of the most prevalent and severe forms of dystonia, manifesting in childhood and persisting throughout life. Mutations in the human TOR1A gene, encoding torsinA, are associated with EOD. TorsinA is an Endoplasmic reticulum (ER) - Nuclear envelope resident protein, that belongs to the AAA ATPases superfamily. TorsinA has been implicated in several cellular processes including cell polarity, nuclear transport, migration, ER associated degradation, and lipid metabolism. In contrast to extensive studies on torsinA function, studies on regulation of TOR1A expression are limited. Here, we report that selective inhibitors of the glycogen synthase kinase 3 beta (GSK3β) repress TOR1A expression. The regulation is on the transcriptional level, and is specific for the human versus the mouse gene. GSK3β is a multifunctional kinase, involved in WNT-β-catenin-LEF1/TCF, Hedgehog, Notch, and other signaling cascades. Aberrant GSK3β regulation is implicated in malignancies, cardiovascular and neurological disorders. The TOR1A promoter bears consensus LEF1/TCF and Notch-responsive transcriptional elements, which could mediate the observed GSK3β effect on TOR1A expression. Even thought the precise GSK3β-TOR1A cascade remains to be elucidated, the present study uncovers a relationship between GSK3β and TOR1A, extends the list of GSK3β target genes, identifies the first small molecules regulating TOR1A expression, and inspires research on the downstream effects of GSK3β-mediated reduced expression of wild type and EOD-associated forms of torsion.

1-D-90 Difference in temperature between home and experimental tanks alters behavioral responses in zebrafish.

Benjamin Tsang[1], Hayden Chow[2], Hifsa Zahid[1], Rida Ansari[1], Richard Chi Yeung Lee[1], Robert Gerlai[1]

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

Zebrafish have recently started to gain momentum as an alternative animal model for behavioral phenotyping due to its versatility, ease of use, and of maintenance over rats and mice. However, a number of environmental parameters that are vital for normal function and behavior has yet to be systematically explored and tested. Most studies do not disclose testing tank parameter information, and the effects of the transfer of zebrafish from home tank to testing tank is also largely unknown. We argue that there is a need to consider water parameters of zebrafish in their housing and testing environments. In the current study, we examined the effects of transferring zebrafish from their home tank set to 28°C to experimental tanks whose water was set to either 24, 26, 28, 30 or 32oC. Our time course analyses conducted over 20-minute recording sessions revealed temperature dependent behavioral responses, including locomotor activity, turn angle, distance to bottom and freezing. The results of our study demonstrate the importance of home vs experimental tank temperature as a potential confounding variable in behavioral research with zebrafish.

1-D-91 You must stop balancing before you can walk

Romain Tisserand[1], Christopher Dakin[2], Machiel Van der Loos[1], Elizabeth Croft[1], Timothy Inglis[1], Jean-Sebastien Blouin[1]

[1]University of British Columbia, [2]Utah State University

Optimal feedback control theory indicates that the maintenance of a specific postural configuration, such as standing balance, or a movement pattern, such as locomotion, operates under a distinct control policy. Hence, transitions between posture and movement require disengagement of the current control policy before the engagement of a new one. We investigated this hypothesis by examining the continuity of vestibular-motor mapping during transitions between standing balance and locomotion. Ten healthy male subjects initiated and terminated locomotion, at their preferred walking speed, while exposed to a continuous electrical vestibular stimulus (EVS). Ground reaction forces (GRFs) were recorded before, during and after the transition from quiet standing to locomotion (gait initiation) and from locomotion

to quiet standing (gait termination). The relationship between the EVS and the GRFs was quantified using time-frequency coherence. We observed a coherence null period preceding the onset of anticipatory postural adjustments during the initiation of locomotion and during the step prior to the termination of locomotion. These results suggest a discrete change between motor control policies permitting disengagement of the current motor policy to make way for the next, as predicted by optimal feedback theory, during locomotor transitions. Ultimately, we demonstrate that humans must "stop balancing" before they can walk and "stop walking" before they can stand.

1-D-92 Assessing cognitive-motor integration in middle-aged athletes: the effects of dementia risk & concussion

Andrea Cavaliere[1], Diana Gorbet[1], Lauren Sergio[1]

[1]York University

This project investigates the relationship between dementia risk and concussion history in a physically active, middle-aged adult (male & female) population between the ages of 30 and 65. These participants are grouped into the following: family history of dementia, history of sustained concussion(s), both histories, and controls (no history of either). Previous work in our lab found that those with dementia or concussion history performed poorly when asked to make skilled movements while thinking concurrently (cognitive-motor integration, CMI). We conducted a CMI assessment using a computer tablet-based task; data collected includes various kinematic outcomes. Participants also completed a questionnaire on various lifestyle factors like physical fitness and smoking history. We predict that those with either a concussion history or family history of dementia will perform poorly than controls, and that this effect will be exacerbated in those with both histories. The data collected will expand current research on rule-based skill assessment that can identify functional CMI impairments before current clinical signs of dementia are observed (or after current signs of concussion resolution are observed). On an exploratory basis, these data will provide insight into lifestyle factors that may affect CMI in middle-aged adults, an ability often important for functioning safely at work and sport. Our preliminary data suggests that there is a significant difference between groups with regards to the percentage of corrected trials completed on the CMI task [$F(3,18)= 5.64$, $p= .007$].

1-D-93 IGF-1 activates AMPK to bidirectionally regulate mitochondrial function in adult sensory neurons

Mohamad-Reza Aghanoori[1], Darrell Smith[2], Mohammad Golam Sabbir[2], Paul Fernyhough[1]

[1]Division of Neurodegenerative Disorders, St Boniface Hospital Albrechtsen Research Centre and Depart, [2]Division of Neurodegenerative Disorders, St Boniface Hospital Albrechtsen Research Centre

There is impaired growth factor signaling allied with down-regulation of AMP-activated protein kinase (AMPK) activity and mitochondrial function in dorsal root ganglia (DRG) in animal models of type 1 and type 2 diabetes exhibiting peripheral neuropathy. Thus, we hypothesized that loss of insulin-like growth factor-1 (IGF-1) signaling in diabetes contributed to depressed AMPK activity and mitochondrial function in DRG neurons. Adult DRG neurons were cultured from age-matched control or streptozotocin-induced type 1 diabetic rats. Neurons were treated with/without 10nM IGF-1 and underwent qRT-PCR and Western blotting for analysis of gene expression. Mitochondrial DNA (mtDNA) quantity was determined and mitochondrial respiration quantified using the Seahorse XF24. Dysregulation of genes including IGF-1, AMPKα2, ATP5a1 (subunit of ATPase), peroxisome proliferator-activated receptor γ coactivator-1β was observed in cultured DRG neurons derived from diabetic vs. control rats at the mRNA level which were normalized by IGF-1. IGF-1 significantly ($P<0.05$) increased phosphorylation of Akt, P70S6K, AMPK and acetyl-CoA-carboxylase (ACC) enzymes, and elevated mtDNA levels and electron transport chain (ETC) proteins. Inhibition of AMPK by compound C or AMPKα1 siRNA specifically suppressed IGF-1 upregulation of pACC and mitochondrial respiration. In comparison, AMPKα2 siRNA depressed IGF-1 upregulation of ETC proteins. Therefore, IGF-1 acts through two isoforms of AMPK to optimize mitochondrial phenotype and may represent an effective therapeutic option in diabetic neuropathy.

1-D-94 Regeneration of Auditory Neurons by Reprogramming Endogenous Spiral Ganglion Glial Cells

Steven Meas[1], Teppei Noda[2], Koji Nishimura[2], Alain Dabdoub[1]

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

Primary auditory neurons form the neural connection between the inner ear and the central nervous system. One of the leading causes of hearing loss is the degeneration of primary auditory neurons, which is caused by exposure to noise, ototoxic drugs and/or aging. Auditory

neurons do not have the capacity to regenerate after injury and currently there are no treatments that can remedy their loss. Therefore, there is an unprecedented need to find ways to replace auditory neurons in the spiral ganglion, the location of auditory neuron soma. Reprogramming endogenous glial cells within this niche into auditory neuron-like cells offers tremendous clinical potential to restore hearing. Results from our laboratory indicate that neonatal and adult glial cells can be reprogrammed into induced neurons in vitro when transfected with the pioneer transcription factor Ascl1 and neural differentiation factor NeuroD1. Induced neurons exhibit neuronal morphology and express several key markers of neuron identity. They extend projections towards hair cells, the mechanosensory transducers within the cochlea, and cells of the cochlear nucleus in the brain, when co-cultured. RNAseq data further indicates that these cells resemble auditory neurons at the level of the transcriptome. In ongoing work, we hypothesize that spiral ganglion glial cells can be virally reprogrammed in vivo. We hypothesize that by inducing spiral ganglion glial cells to convert into neurons in vivo, these cells will have the ability to functionally innervate the endogenous targets to restore hearing.

1-D-95 Effects of Dynorphin on Spinal Network Activity

Prince Ozogbuda[1], Patrick Whelan[1]

[1]University of Calgary

Several studies have identified orexin as a potential therapeutic neuropeptide that exerts robust pro-locomotory effects. However, another study by Muschamp et al. (2014) revealed that orexin is co-packaged and co-released with dynorphin, an inhibitory neuropeptide. Dynorphin, on the other hand, have been shown by several studies to induce paresis upon intrathecal injection. Why then is an inhibitory neuropeptide co-released with an excitatory pro-locomotory neuropeptide orexin, and what is its role? In this study the expression of kappa opioid receptors on motoneurons was demonstrated using RNAscope Assay. The effect of dynorphin on locomotion was studied by observing its effect on fictive locomotion generated in an isolated spinal cord preparation. The application of 1 µM U69,593, a selective KOR agonist was shown to significantly reduce spontaneous activity. Interestingly, the addition of the same 1 µM U69,593 did not stop fictive locomotion; instead, it only reduced the frequency of locomotion. These results suggest that while dynorphin may significantly reduce spontaneous activity in the spinal cord in a low conductance state, it only modulates spinal locomotor network output in a high conductance state. This also explains why the co-release of orexin and dynorphin does not have antagonistic effect. Furthermore, this study is important because the elucidation of dynorphin's

role in enhancing locomotor output coupled with its already established potential to reduce neuropathic pain makes it an enticing therapeutic agent for the treatment of spinal cord injuries.

1-D-96 Nile grass rats as a novel model of protracted type-2 diabetes-induced peripheral sensory neuropathy

Jyoti Singh[1], Saad Yousuf[1], Paige Shelemey[1], Twinkle Joy[1], Haecy Macandili[1], Bradley Kerr[1], Kelvin Jones[1], Yves Sauve[1], Klaus Ballanyi[1], Christine Webber[1]

[1]University of Alberta

Peripheral sensory neuropathy (PSN) is a devastating complication of type-2 diabetes (T2D) marked by several pathological features such as numbness, mechanical allodynia, hyperalgesia, paresthesia or altered temperature sensitivity. Current animal models have been useful in demonstrating T2D pathogenesis; however, genetic complexity, pharmacological alteration, and rapid T2D progression makes them difficult to select and mimic T2D pathogenesis at preclinical stages. The African Nile grass rat (NGR) is an excellent model for T2D because, similar to humans, the onset is metabolic instead of experimental. Simply feeding male NGRs with a high calorie, low fiber diet (chow) develop T2D whereas NGRs fed on a high fiber, low fat diet (Hfib) remain healthy. Thus we are establishing the NGR as a novel diet-induced T2D-PSN model. Similar to human patients, T2D NGRs have epidermal denervation and motor nerve conduction velocity. Specifically, chronic T2D leads to hyposensitivity to both painful mechanical and heat stimulation compared to controls. At the dorsal root ganglion (DRG), T2D NGRs have activation of the surrounding satellite glial cells in the DRG neurons as demonstrated by increased glial fibrillary acidic protein (GFAP) expression. Furthermore, there was an upregulation of voltage-gated sodium channel variants Nav 1.7 and Nav 1.9 mRNA and protein levels in T2D NGRs. Electrophysiologically recorded Aδ- and C-fibres have decreased electrical and mechanical excitation thresholds. T2D NGR serves as a model of PSN presenting with classic symptoms that parallels human T2D-PSN.

1-D-97 Neural correlates of sensory and motor information retained in parietal area 5 for memory-guided obstacle avoidance in the walking cat

Carmen Wong[1], Stephen Lomber[1]

[1]*The University of Western Ontario*

In complex environments, information about surrounding obstacles stored in working memory is used to coordinate movements for avoidance. In quadrupeds, this memory system is important for guiding hindleg stepping over an obstacle once it has passed under the body. In cats, deactivation of parietal area 5 incurs substantial memory deficits, precluding successful obstacle avoidance. To examine the neural correlates of obstacle memory, microelectrode arrays were chronically implanted to record area 5 activity during obstructed and unobstructed locomotion in cats. In obstructed trials, forward locomotion was paused either after foreleg clearance with the obstacle between the fore- and hindlegs (FH trials), or after only one hindleg cleared the obstacle (HH trials). In a subset of isolated units, activity was selectively elevated when locomotion was paused in obstructed trials. These units demonstrated increased firing during the delay period of FH trials, HH trials, or both. As either one or both hindleg steps must be elevated once walking resumes in HH or FH trials, respectively, units with sustained activity selective to only one type of obstructed trial may be responsible for retaining the different impending motor commands. Conversely, sustained activity in both FH and HH trials may represent retained sensory information about the obstacle pertinent to both types of obstructed trials. Altogether, both sensory and motor information retained in parietal area 5 may be necessary for successful memory-guided obstacle avoidance.

1-D-98 Pain resolution and motor recovery following peripheral nerve injury: how can exercise help?

Charlie Kwok[1], Kyle Mayr[1], Patrick Whelan[1], Tuan Trang[1]

[1]University of Calgary

Neuropathic pain affects 47 million people worldwide and is difficult to treat. Clinical studies show pain improvements with physical therapy. In rodents significant pain and motor deficits occur following nerve injuries, further indicating an interaction between the motor and sensory systems. We aim to study the interactions between the motor and sensory circuits within the spinal cord, and provide a mechanistic understanding for the benefits of exercise on neuropathic pain. We hypothesise that exercise modulates neuroinflammation, which in turn promotes activity-dependent motor recovery and pain reduction. Using the spared nerve injury (SNI) model in male mice (C57/B6), pain and motor behaviours are quantified with von Frey hair tests for mechanical allodynia, and a ladder rung test for gait abnormalities and paw placements, at baseline and up to day 28 after SNI. We observed significant pain and motor deficits, with motor

recovery preceding pain resolution. Next, using CD11b immunoreactivity, we observed microglial activation in both the spinal dorsal and ventral horns. Colocalisation of CD11b with ChAt (marker of motoneurons) and GAD (marker of GABAergic interneurons) showed significant anatomical changes on spinal sensorimotor circuits between sham and SNI mice. In a separate cohort of mice, we will next investigate the effects of wheel-running (4 weeks before SNI) on pain and motor behaviours, and anatomical changes in CD11b, GAD and ChAt immunoreactivity.We conclude that significant sensorimotor changes occur following SNI, which may be augmented by wheel running.

1-D-99 Asymmetric Vestibular Function in Adolescents with Idiopathic Scoliosis

Emma Woo[1], Gunter Siegmund[2], Christopher Reilly[3], Jean-Sebastien Blouin[1]

[1]University of British Columbia, [2]MEA Forensic Engineers & Scientists, [3]BC Children's Hospital

Adolescent Idiopathic Scoliosis (AIS) has no single well-defined cause. Instead, studies point to multifactorial causes that include sensorimotor dysfunction, one of which may be asymmetric vestibular function. In tadpoles, unilateral labyrinthectomy results in spinal curvature that is similar to scoliosis and persists into adulthood (Lambert et al., 2009). Further research characterizing unilateral and bilateral vestibular function in AIS patients and controls is required. 10 AIS patients (8 females, 14.1±1.5 years) (mean±SD) and 4 controls (3 females, 14.8±1.5 years) were exposed to kinetic rotations (slow seated rotations) and virtual rotations (monaural and binaural electrical vestibular stimulation, EVS) at 0.1Hz. Using a forced-choice paradigm, subjects indicate which direction they rotated (or perceived to rotate) after each trial. A Bayesian adaptive procedure modulated the stimulus intensity to find a threshold where subjects correctly identified the rotation direction 69% of the time. An asymmetry index (AI = LR_difference/LR_average) quantified the asymmetry in unilateral vestibular perception. Our preliminary results indicate 8 of 10 patients had an asymmetric vestibular perception threshold that was larger than controls. AI was 0.32±0.11 in patients and 0.088±0.021 in controls. Kinetic (2.17±0.54°/s vs. 1.98±0.58°/s) and binaural EVS thresholds (1.14±0.43 mA vs. 0.98±0.24mA) did not differentiate patients from controls. Our results provide promising preliminary evidence of asymmetric vestibular function in AIS.

1-D-100 Influences of Emotional modulation on human brainstem pain-signaling pathways

Jocelyn Powers[1], Patrick Stroman[1], Natasha Talwar[1]

[1]Queen's University

Pain is a subjective unpleasant experience that includes discriminative and affective components and can be modulated by one's cognitive or emotional state. Emotion is thought to modulate pain perception through descending inhibition mediated by specific brainstem structures. The neural mechanism has not been observed in humans, as most studies have been conducted in animals and tissue preparations. The purpose of this study was to determine the modulatory effect of emotion on brainstem pain signaling regions. We hypothesize that, as part of the limbic system, hypothalamic input will influence pain-related signaling in relation to one's emotional state. This was tested with structural equation modeling (SEM) using fMRI data from three previous pain studies. The model uses a multi-linear regression to approximate the covariance between blood-oxygen-level-dependent (BOLD) signal changes across two or more brainstem areas. A control study without emotional modulation was compared against two studies with emotional modulation of evoked heat pain. SEM was used to model significant networks of connections between the hypothalamus (Hyp), periaqueductal gray (PAG), nucleus raphe magnus (NRM) and nucleus tractus solitarius (NTS). Results of the analysis indicate that emotion may modulate pain perception through a Hyp-PAG connection present only in the emotional modulation studies. Connectivity between areas in the chosen network was dynamic and varied across periods before, during and after pain stimulation, indicating more complex, coordinated activity than previously understood.

1-D-101 Deficits in global motion perception and functional MT+ responses in enucleated children

Benjamin Dunkley[1], Arijit Chakraborty[2], Brenda Gallie[1], Daphen McCulloch[2], Margot Taylor[1], Ben Thompson[2]

[1]Hospital for Sick Children, [2]University of Waterloo

Subsequent to early-life enucleation, the removal of an eye, adults exhibit perceptual asymmetries in global motion coherence thresholds (MCT) biased for nasalward motion in the absence of other visual dysfunction. Little is known about the functional neurophysiology in regions that process visual motion and might underlie this deficit. We used MEG, psychophysics

and fMRI to explore functional changes in motion perception in children, predicting that low-frequency event-related desynchronisation (ERD) in MT+, but not in V1, would explain motion deficits related to early-life enucleation. Data were acquired from seven monocular enucleates (ME; 6-12 yrs) and ten binocular controls (BC) matched on age. MEG data were collected whilst viewing a full-coherence motion field and time-frequency analyses were performed on visual cortices (from an fMRI MT localiser and V1). Visual acuity, contrast sensitivity, and MCT were measured using alternative forced choice tests. fMRI data were collected whilst participants passively viewed a radial motion dot-field. There were no group differences in acuity or contrast sensitivity, but there was a difference in the ratio of naso-temporal MCT. The fMRI localiser identified bilateral MT+. Alpha and beta ERD in V1 to motion for BC vs ME was largely equivalent. However, MT+ exhibited differential alpha-beta ERD when contrasting groups, with less suppression in ME compared to BC. These results suggests visual motion deficits may reside in MT+, highlighting the importance of binocular input for normal development of motion cortex and perception.

1-D-102 Advillin is expressed throughout the autonomic nervous system

Diana Hunter[1], Brittney Smaila[1], Douglas Lopes[2], Franziska Denk[2], Matthew Ramer[1]

[1]University of British Columbia, [2]King's College London

Expression of the actin-binding protein advillin has been described as specific to sensory neurons, and has thus been used repeatedly to drive genetic recombination therein. Here we characterize expression amongst sensory neurons, and show advillin expression in several other tissues. We first validate an advillin antibody against advillin promoter driven EGFP expression and advillin mRNA expression (using available in situ hybridization data). In the dorsal root ganglion, advillin is enriched in the non-peptidergic class of nociceptors. We also show that advillin expression, and advillin promotor-driven EGFP and Cre-recombinase expression, occurs in multiple tissues including the dorsal habenula of the epithalamus, endocrine cells of the gut, Merkel cells in the skin, and most strikingly, throughout the autonomic nervous system (sympathetic, parasympathetic, and enteric neurons) in mice, rats, and non-human primates. In the mouse pelvic ganglion, advillin immunoreactivity is most intense in pairs of small neurons, and concentrated in spine-like structures on the axon initial segment contacted by sympathetic preganglionic axons. In autonomic targets (iris and blood vessels), advillin is distributed along cholinergic parasympathetic axons and in tyrosine hydroxylase and dopamine--hydroxylase-positive sympathetic varicosities. These results not only indicate advillin-driven genetic

manipulation as a potentially useful tool for studying numerous cell types, but also warrant caution in interpreting previous studies in which advillin is cited as sensory neuron-specific.

1-D-103 The influence of visual stimulation and systemic metabolite availability on extracellular fluctuations of glucose and lactate in the mouse visual cortex

Alexandria Beland[1], Claude Messier[1]

[1]University of Ottawa

We measured the extracellular glucose and lactate in the primary visual cortex of the mouse using electrochemical electrodes to examine the impact of systemic injections of lactate and fructose on the brain extracellular glucose and lactate changes observed during visual stimulation. We found that simple stimulation using a flashlight produced a decrease in visual cortex extracellular glucose and an increase in extracellular lactate. Similar results were observed following visual stimulation with an animated movie or the presentation of a novel object. Specificity of these observations was confirmed by the absence of extracellular glucose and lactate changes when the mice were presented a second time with the same object. Previous experiments have shown that systemic injections of fructose and lactate lead to an increase in blood lactate but no change in blood glucose while they both increase brain extracellular glucose but they do not increase brain extracellular lactate. When mice were visually stimulated after they had received these injections, we found that lactate, and to a slightly lesser degree fructose, both reduced the amplitude of the changes in extracellular glucose and lactate that accompanied visual stimulation. Thus, neural activation leads to an increase in extracellular lactate and a decrease in extracellular glucose. Novelty, attentional resources and availability of metabolic fuels modulate these fluctuations. The observations are consistent with a modified view of brain metabolism that takes into account the blood and brain glucose availability.

1-E-104 Circadian Rhythm Alters Anxiolytic Effects of Ethanol on Zebrafish Behaviour

Rida Ansari[1], Amna Azhar[2], Benjamin Tsang[1], Robert Gerlai[1]

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

Circadian rhythms impose temporal order throughout the brain and body, regulating physiological mechanisms and behaviours within a period of 24 hours. Genetic and

neuroendocrine mechanisms under control of this system regulate rhythms of melatonin secretion, structural synaptic plasticity, locomotor activity and sleep. The zebrafish (Danio rerio) is becoming an increasingly popular model for circadian studies, and is equipped with circadian regulatory mechanisms similar to those of flies and mammals. However, little is known about the interaction of circadian rhythms and pharmacologically-induced behavioural responses in zebrafish. We argue that circadian rhythms could alter ethanol-induced changes in anxiety-like behaviours in zebrafish. The objective of this study was to examine the effects of acute exposure (0%, 1% v/v) to ethanol, an anxiolytic substance, on zebrafish behavioural responses during the beginning and end of typical testing times (close to the start and end of the light phase of the photoperiod), i.e. between 9:00 to 11:00 and 17:00 to 19:00 hours. Our time course analyses conducted over 20-minute recording sessions revealed circadian rhythm dependent behavioural responses: zebrafish exposed to 1% v/v ethanol showed reduced bottom dwelling behaviour between the 17:00 to 19:00 as compared to those tested earlier in the day (9:00 to 11:00). The results of our experiment highlight the importance of circadian rhythms as a potential confounding variable in behavioural and pharmacological research with zebrafish.

1-E-105 Astrocyte-derived ACBP/DBI activates the hypothalamic melanocortin pathway to regulate feeding and energy homeostasis.

Khalil Bouyakdan[1], Chloé Chrétien[2], Demetra Rodaros[3], Fabienne Liénard[2], Érik Biron[4], Luc Pénicaud[2], Xavier Fioramonti[5]

[1]Centre de recherche du CHUM, [2]Université de Bourgogne, [3]CRCHUM - Univeristé de Montréal, [4]CHUL, [5]Université de Bordeaux

Unsaturated fatty acid (U-FA) can act in the arcuate nucleus (ARC) of the hypothalamus to modulate feeding and peripheral glucose homeostasis. Recent data in astrocytes show that Acyl-CoA Binding Protein (ACBP) regulates U-FA metabolism and that octadecaneuropeptide (ODN), an endozepine derived from its cleavage, modulates feeding and peripheral glucose homeostasis. It is thought that the anorectic effect of ODN involves the melanocortin pathway, a key player in the hypothalamic control of energy balance. Thus we aim to determine how ODN activates proopiomelanocortin (POMC) neurons in the ARC and in turn, modulate energy homeostasis in vivo. Using electrophysiological recordings in brain slices from POMC-eGFP mice, we show that ODN selectively increases the firing rate of POMC neurons in the ARC independently of GABAAR inhibition. Calcium imaging recordings in dissociated primary hypothalamic neurons show that the antagonist of the metabotropic ODN receptor inhibits

ODN-induced calcium oscillations. Our astrocyte-specific deletion of ACBP confirms that a disruption of the ODN-POMC-MC4R pathway leads to an exacerbated diet-induced obesity and altered feeding behaviors. Finally, viral mediated rescue of ACBP expression in the ARC alleviates the effects of astrocyte-specific deletion and ARC-specific ACBP overexpression decreases feeding and weight gain. These findings highlight the importance of ODN in the regulation of feeding through the melanocortin pathway and open new research avenues related to the hypothalamic control of energy balance by astrocyte derived-endozepines.

1-E-106 Local blockage of cannabinoid signalling attenuates the orexigenic effect of ghrelin when it is infused into the VTA

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

[1]Carleton University

Ghrelin increases feeding by activating growth hormone secretagogue receptors (GHSRs) in feeding related brain regions such as the hypothalamus (HYP) and ventral tegmental area (VTA). Similarly, endocannabinoids (eCBs) also stimulate appetite within these regions by binding cannabinoid receptors (CB-1Rs). Within the HYP, ghrelin and eCB systems interact and depend on one another to promote feeding behaviours. Recent data suggests that a similar interaction may be important for regulating feeding behaviours within the VTA of rats. We hypothesised that a functional eCB system within the VTA would be essential for intra-VTA ghrelin induced feeding. We reasoned that pre-treating rats with intra-VTA rimonabant before infusing ghrelin within the VTA would block the ability of ghrelin to promote food intake. To this end, we implanted male rats with cannulae aimed at the VTA (ML= 2 mm, DV= 7.8 mm, AP= 5.6 mm) and assigned them to one of four treatment groups: vehicle/saline, rimonabant (0.5 µg)/saline, vehicle/ghrelin (1 µg), rimonabant (0.5 µg) /ghrelin (1 µg). On test days, rats were pre-treated with vehicle or rimonabant (0.5 µl) 30 minutes before infusion with either saline or ghrelin (0.5 µl). Acute food intake and locomotor activity of each animal was subsequently monitored. Locomotor activity did not differ between treatment groups; however, inhibition of the eCB system within the VTA attenuated intra-VTA ghrelin induced feeding. These data suggest that the interaction between ghrelin and eCB systems within the VTA is important for regulating food intake.

1-E-107 A Genetic Variant of Fatty Acid Amide Hydrolase Regulates the Opposing Crosstalk between Leptin and Glucocorticoids in the Context of Feeding

Georgia Balsevich[1], Gavin Petrie[1], Arashdeep Singh[1], Martin Sticht[1], Stephanie Borgland[1], Prasanth Chelikani[1], Matthew Hill[1]

[1]University of Calgary

Fatty acid amide hydrolase (FAAH) is the primary enzyme responsible for the degradation of the endocannabinoid anandamide (AEA). FAAH-AEA signaling plays an important role in the regulation of energy homeostasis whereby its activation promotes feeding, energy storage, and ultimately weight gain. Human genetic studies have identified a common single nucleotide polymorphism (SNP) in the FAAH gene (FAAH C385A; rs324420), which has been associated with reduced FAAH expression, increased anandamide levels, and a higher risk to develop obesity. Nevertheless, it remains unknown how this FAAH variant affects whole body energy balance. Therefore, we examined whether the common FAAH C385A SNP affects the metabolic actions of leptin and glucocorticoids, two key counter-regulators of energy homeostasis, using a novel C385A knock-in mouse model, which recapitulates the common human variant. We found that FAAH A/A mice, who present decreased FAAH expression, are less responsive to leptin's anorectic effects following an overnight fast. By contrast, FAAH A/A mice were more susceptible to glucocorticoid-induced hyperphagia, weight gain, and changes in glucose tolerance. There was no effect of the FAAH C385A polymorphism on either glucocorticoid- or leptin-dependent changes in substrate utilization or energy expenditure. These findings suggest that the FAAH C385A polymorphism mediates a shift in balance between orexigenic and anorectic signals, increasing the sensitivity to glucocorticoid's orexigenic effects and decreasing the sensitivity to leptin's anorectic effects.

1-E-108 Growth differentiation factor 15 modulates the activity of neurons involved in energy balance

Nick Simpson[1], Hanna Grover[1], Alastair Ferguson[1]

[1]Queen's University

Growth differentiation factor 15 (GDF-15), also known as macrophage inhibitory cytokine 1, is a protein belonging to the transforming growth factor beta superfamily and is upregulated in many diseases, such as heart disease and cancer. Intriguingly, GDF-15 has been shown to mediate cancer-induced anorexia in mice by acting centrally, suggesting a role for GDF-15 in the

regulation of energy homeostasis. Recently, multiple independent studies identified GDNF receptor alpha like (GFRAL) as the receptor responsible for the anorexic effects of GDF-15. This receptor has been identified in regions of the central nervous system known to regulate energy homeostasis, including the area postrema (AP) and the nucleus tractus solitarius (NTS). Furthermore, lesion of the AP and NTS completely abolishes the anorexic effect of GDF-15. However, the neuronal mechanisms by which GDF-15/GFRAL are able to influence energy homeostasis through these regions remains unexplored. Therefore, we performed Ca2+ imaging and extracellular electrophysiological recordings on AP and NTS neurons derived from male Sprague-Dawley rats. Bath application of 10 nM GDF-15 increased intracellular Ca2+ in 39% of AP neurons (n = 9/23; Δ F/Fo = 0.34 ± 0.05). Furthermore, 10 nM GDF-15 increased and decreased the firing rate by 50% and 10% of NTS neurons, respectively. These data suggest that GDF-15 is able to modulate the activity of a proportion of neurons from each region. Future studies should continue to elucidate the cellular and circuit mechanisms through which GDF-15 regulates energy homeostasis.

1-E-109 Sexually dimorphic endocannabinoid-mediated plasticity in the VTA after acute fasting

Nathan Godfrey[1], Min Qiao[1], Stephanie Borgland[1]

[1]University of Calgary

Dopamine neurons in the ventral tegmental area (VTA) are important for energizing goal directed behaviour towards food. These neurons are sensitive to changes in metabolic states as they respond to peripheral peptides that signal hunger, satiety or stress. Acute fasting increases the incentive motivation for food as well as the mobilization of energy stores by increasing corticosterone. We tested if there were sexually dimorphic effects on dopaminergic synaptic transmission in the VTA after acute (16h) fasting. We found no changes in amplitude or frequency of mIPSCs or mEPSCs or changes to the AMPAR/NMDAR ratio following fasting. However, we found endocannabinoid-mediated depolarization-induced suppression of inhibition (DSI) was significantly greater in females than male control mice. Further, DSI was significantly increased in male but not female fasted mice. In contrast, depolarization-induced suppression of excitation (DSE) was increased in female but not male fasted mice. In attempt to determine the VTA input that is responsible for this change, we selectively photostimulated fibers in the VTA projecting from excitatory cells of the Lateral Hypothalamus (LH). We show here that, although the LH projection is sensitive to endocannabinoids, the changes that occur

following fasting are not seen in this projection. Taken together, these results demonstrate that fasting suppresses excitatory inputs to the VTA in females and inhibitory inputs in males, indicating that the mesolimbic circuit of males and females respond differently to energy deprivation.

1-E-110 Phoenixin activates nucleus of the solitary tract neurons and this excitatory effect is abolished in chronic stress-like conditions

Hanna Grover[1], Alastair Ferguson[1]

[1]Queen's University

Phoenixin (PNX) is a recently described neuropeptide initially found to modulate gonadotropin-releasing hormone receptor expression within the anterior pituitary and contribute to estrous cyclicity. Since its discovery however, PNX has been implicated in a diverse range of physiological activity, including anxiety-like behaviour, nociceptive responses, memory retention, and food intake. With robust expression to compliment this variety of physiological action, it is clear that PNX plays a pleiotropic role in whole-organism homeostasis. One of many areas in the brain with high expression of PNX and its receptor is the nucleus of the solitary tract (NTS), a critical integrating centre for autonomic function including cardiovascular, gastrointestinal, respiratory, and gustatory processes. Using both extracellular and whole-cell current clamp recording techniques in a slice preparation, we sought to characterize the effects of PNX on the activity of NTS neurons. We used extracellular recordings to show that PNX increased firing frequency in 32% of male rat NTS neurons (n=98), and whole cell patch clamp techniques to show that the peptide depolarized 50% of neurons (n=40). Interestingly, after rats were housed under chronic stress-like conditions, activation of almost all NTS neurons by PNX was completely eliminated (n=7/137 cells responsive to PNX). These experiments thus demonstrate for the first time the effects of PNX on the activity of NTS neurons and provide unique insight into a potential mechanism for stress-induced disruption of central autonomic function.

1-F-111 Effect of PGE inhibition on striatal neuroinflammation in 6-OHDA lesion

Temitope Adu[1], Musa Mabandla[1]

[1]University of KwaZulu- Natal

Background: Neuroinflammation plays a role in the micro-environment disturbance in Parkinson's disease (PD). Cytokines and non-cytokines induced pathways affect glial cell activation following injury. Prostaglandin E2 has been implicated in the non-cytokine response to inflammation. This raises the question of whether manipulation of the inflammatory response pathways could lead to therapeutic interventions for PD. In this study, we investigated the role of PGE2 inhibition, pro-inflammatory cytokine concentration and gliosis in PD rats. Methods: Male Sprague-Dawley rats were lesioned stereotaxically with 6-OHDA. Bromelain (Br) which inhibits PGE2 was used to treat a subset of the rats. Pre-lesion, 24 & 72hrs post lesion behavioural assessments using open field, cylinder and step tests were carried out. Systemic and Striatal concentration of pro-inflammatory cytokines and the quantification of CD11b/CD86 as a measure of glial cell activation were assessed. Findings: 6-OHDA injection resulted into marked motor impairment which was alleviated by pre-lesion and 72hrs post lesion bromelain treatment. Br treatment also resulted in suppression of both systemic and striatal pro-inflammatory mediators (IL-1β, IL-6 & TNF-α)as well as changes indicative of suppression of gliosis. Conclusion: Br treatment reveals interconnectivity between cytokines and non-cytokines mediated neuroinflammatory pathways suggesting suggesting that PGE2 inhibition plays a role in protecting against dopamine neurodegeneration and may be considered as part of therapeutic strategy to attenuate PD progression.

1-F-112 Involvement of orexinergic receptors within the nucleus accumbens in stress- and drug priming-induced reinstatement of morphine-seeking behaviors in the rats

Abbas Haghparast[1], Marjan Sahafzadeh[2], Zahra Farzinpour[3]

[1]Neuroscience Research Center Shahid Beheshti University of Medical science, [2]Rheinische Friedrich-Wilhelm University of Bonn, [3]University of Science and Technology of China

Orexin plays a key role in mediating stress-induced drug relapse. However, the role of different types of orexinergic receptors that modulate stress-induced drug seeking remains unknown. The nucleus accumbens (NAc) has an important role in the reward system and receives orexinergic projections of the lateral hypothalamus. Therefore, in the present study, we used conditioned place preference (CPP) to investigate the role of orexinergic receptors in the NAc in morphine priming- induced reinstatement and the effect of two models of stress include food deprivation (FD) and forced swim stress (FSS) on drug reinstatement. In order to induce CPP, the animals were given morphine (5 mg/kg; sc) for three conditioning days. The priming dose of morphine (1 mg/kg, sc) reinstated the extinguished morphine-induced CPP. The extinguished rats were

tested for reinstatement following the 24-h FD condition or FSS for 6 min, and in other groups, the animals were stereotaxically given intra-NAc administration of SB334867 (0.1, 1 and 10 nM /0.5 µl DMSO) or TCS OX2 29 (1, 5 and 25 nM/0.5 µl DMSO) as an orexin-1 or orexin-2 receptor antagonist respectively, just before application of FD or FSS in separated groups. Our results showed that not only these two types of orexin receptors in the NAc remarkably attenuate morphine-induced reinstatement, but also inhibited the stress-induced reinstatement after application of FD and FSS models. These findings indicate that the orexinergic system in the NAc is a fundamental role in the effect of stress on reinstatement of morphine-seeking behaviors.

1-F-114 Effect of orexin receptor 1 blockade in the anterior cingulate and orbitofrontal cortex on cost and benefit decision-making

SARA KARIMI[1], Abbaa Haghparast[2], Gholam Ali Hamidi[1]

[1]Kashan University of medical sciences, [2]Shahid behesti University of medical science

Orexin neurons are discretely localized within the lateral hypothalamus and have widespread projections to the whole brain. In addition, several lines of evidence specify that orexins may also participate in the regulation of a variety of affective and cognitive processes. Delay- based decision- making is mediated largely by the orbitofrontal cortex (OFC) and effort based decision- making is controlled with anterior cingulated cortex (ACC). Hence, in the present study, we conducted a series of experiments to clarify the role of OX1rin the mPFC (ACC and/or OFC) in cost and benefit decision- making. The rats had been trained in a delay and/or effort based form of cost-benefit T-maze decision making task. Two goal arms were different in the amount of accessible reward. The animals could choose high reward arm (HR arm) and pay cost to achieve large reward or obtain a low reward in the other arm without cost (LR arm). Before surgery, all animals were selecting the HR arm on almost every trial. During test days, the rats received local injections of either DMSO 20% /0.5µl, as vehicle, or SB334867 (3,30, 300 nM/0.5µl), as selective OX1rantagonist, within the ACC and/or OFC. Our results showed the bilateral microinjection of SB334867 into ACC and/or OFC changed the preference to a low but immediately available reward, indicating the role of OX1 receptors in cost and benefit decision-making. These results imply that OX1receptors in the mPFC have a crucial role for allowing the animal to evaluate and pay the cost to acquire rewards.

1-F-115 Involvement of D1-like dopaminergic receptors in the nucleus accumbens in modulation of formalin-induced orofacial pain

Amirhossein Pirasteh[1], Abbas Haghparast[1]

[1]Neuroscience Research Center Shahid Beheshti University of Medical science

The role of dopaminergic system in modulation of several kinds of nociception has been established. The present study aims to investigate the role of D1-like dopamine receptors in the nucleus accumbens (NAc) in modulation of antinociceptive responses induced by chemical stimulation of the lateral hypothalamus (LH) in animal model of orofacial pain. Thirty four male Wistar rats were unilaterally implanted with two cannulae into the lateral hypothalamus (LH) and NAc. Intra-LH microinjection of carbachol (250 nM/0.5µl saline), a cholinergic receptor agonist, was done 5 min after intra-accumbal administration of different doses of SCH-23390 (0.25, 1 and 4 µg/ 0.5µl saline) as D1-like receptor antagonist. After 5 min, 50 µl of 1% formalin was subcutaneously injected into the upper lip for inducing the orofacial pain. Intra-NAc administration of SCH23390 at two higher doses (1 and 4 µg/ 0.5µl saline) before LH stimulation by carbachol antagonized the antinociceptive responses during both phases of orofacial formalin test. The effects of D1-like receptor antagonism on the LH stimulation-induced antinociception was a little more effective but not significant, at blocking the LH stimulation-induced antinociception during the early phase of formalin test. The findings revealed that there is a direct or indirect neural pathway from the LH to the NAc which is at least partially contributed to the modulation of formalin-induced orofacial nociception through recruitment of D1-like dopamine receptors in this region. Keywords: Orofacial pain; D1-like dopamine receptor; Nucleus accumbens;

1-F-117 Perceptual-cognitive training can enhance cognitive performance in older adults with subjective memory complaints.

Stela Musteata[1], Kaya Yoshida[1], Caroline Spaner[1], Olav Krigolson[1], Brian Christie[1]

[1]University of Victoria

Slower processing speed is frequently reported for older adults with memory difficulties. Speed theory suggests that there is a relationship between these two processes, such that decreased processing speed is associated with decreased memory encoding and subsequently with memory retrieval. The aim of this study is to determine if memory performance can be enhanced in older adults, with subjective memory complaints, by using 3D Multiple Object Tracking (3D-

MOT) to enhance their processing speed. Forty-two subjects were randomly assigned to control and experimental groups and then administered California Verbal Learning Test-II (CVLT-II), D-KEFS Verbal Fluency Test, D-KEFS Trial Making Test. In both groups at baseline poor memory performance was related with slow processing speed. Following 3D-MOT training, the experimental group showed a significant increase in processing speed (e.g., D-KEFS Trail Making Test: Number Sequencing, Number-Letter Switching, Motor Speed; D-KEFS Verbal Fluency: Letter Fluency) and in memory performance (e.g., CVLT-II: Encoding ability, Long Term Memory Recall) compared to the control group. In addition, a significant negative correlation was found between processing speed and 3D-MOT training performance, such that enhanced performance in multiple object tracking is related with faster performance on information processing tasks. These data suggest that training with 3D Multiple Object Tracking may have benefits for cognitive performance in elderly populations.

1-F-118 Imposing Structure on Odor Representations During Learning in OFC and BLA

Peter Wang[1], Cristian Boboila[1], Kristen Lawlor[1], Richard Axel[1]

[1]Columbia University

Odors elicit an unstructured and distributive representation of neural activity in the piriform that encodes odor identity. A restoration of order must therefore be implemented downstream of piriform to elicit an appropriate behavioral output. We performed 2-photon endoscopic imaging during learning in piriform and two downstream associative areas, the basolateral amygdala and orbitofrontal cortex. Piriform odor responses are unaffected by learning. In contrast, before learning, neurons responsive to odor in the BLA and OFC are sparse and non-specific. After learning, over 30% of OFC and BLA neurons exhibit strong responses to the rewarded CS+ odors but do not respond to CS- odors. Moreover, the same population of neurons respond to all CS+ stimuli in both brain regions. Therefore, odor identity in the piriform is transformed by the convergence of sensory and cognitive information to create representations of predictive value in BLA and OFC. We also examined the role of the BLA and OFC in associative learning tasks. Optogenetic silencing of OFC results in a significant impairment in learning simple odor associations. Simultaneous imaging also reveal that OFC inactivation impairs the formation of a representation in BLA. However, if mice have learned previous associations with an intact OFC, silencing the OFC does not affect the learning of new associations. Thus, distributed representations of olfactory learning emerge in multiple brain areas, and the OFC representation appears necessary for the acquisition of task structure during simple associative learning.

1-F-119 An intermittent hypercaloric diet alters gut microbiota, prefrontal cortical gene expression and social behaviours in rats

Amy Reichelt[1], Amy Loughman[1], Ashton Bernard[1], James Dachtler[2], Mukesh Raipuria[3], Thi Thu Hao Vann[1], Robert Moore[1]

[1]RMIT University, [2]Durham University, [3]Federation University

Excessive consumption of high fat and high sugar (HFHS) diets are known to alter reward processing and aspects of behaviour, and change microbiota profiles. Studies in rodents also provide evidence that microorganisms inhabiting the gut influence social behaviour. To further investigate these interactions, the impact of intermittent access to a HFHS diet on social behaviour, gene expression and microbiota composition was examined. Rats were permitted intermittent daily access (2h / day) to a palatable HFHS diet for 28 days across the adolescent period. Social interaction, social memory and novel object recognition were assessed during this period. Following testing, RT-PCR was conducted on hippocampal and prefrontal cortex (PFC) samples. 16S ribosomal RNA amplicon sequencing was used for identification and relative quantification of bacterial taxa. Reduced social interaction behaviours, and impaired social memory and novel object recognition were observed in HFHS diet rats. Reduced levels of monoamine oxidase A (Maoa), catechol-O-methyltransferase (Comt) and brain derived neurotrophic factor (Bdnf) mRNA were observed in the PFC of HFHS diet rats. The relative abundance of a number of specific taxa differed significantly between the two diet groups, in particular, Lachnospiraceae and Ruminoccoceae bacteria, which also predicted social behaviours, novel object recognition performance and Maoa expression. This is the first study to show that limited daily access to HFHS diet alters social behaviour and cognition in rats.

1-F-121 Multiple object tracking training can enhance selective attention and cognitive flexibility in older adults.

Caroline Spaner[1], Stela Musteata[1], Brian Christie[1]

[1]University of Victoria

The objective of this study was to determine whether 3-dimensional multiple object tracking (3D-MOT) could enhance measures of attention and cognitive flexibility as measured by the

Stroop task. The study was performed using a convenience sample of individuals aged 63-87 living in the Greater Victoria region. The Stroop task was administered prior to participants completing 7 training sessions with the NeuroTracker, a 3D-MOT software program. Following completion of the training sessions, the Stroop task was again administered. On-time minus Off-time Stroop scores measured cognitive flexibility and selective attention. Scores were primarily analyzed to determine the significance in score changes post-intervention. A control group completed the Stroop test at week 1 and week 8, without completing the NeuroTracker. Following NeuroTracker training, On-time minus Off-time scores had significantly improved ($M=5.47$, $SD=7.79$, $p=.005$). Significant changes were measured as well in the Off-time conditions ($M=4.66$, $SD=1.61$, $p=.01$), which measured psychomotor speed. Significant changes were measured as well in the On-time conditions ($M=10.24$, $SD=9.25$, $p<.001$), which measured psychomotor speed and cognitive flexibility together. No significant changes were found in any Stroop task measure in the control group. These results suggest that the NeuroTracker may be an effective tool for improving attention and cognitive flexibility in older individuals.

1-F-122 Effects of amyloid beta seeding on Morris water task performance

Sean Lacoursiere[1], Majid Mohajerani[1], Robert Sutherland[1]

[1]University of Lethbridge

Seeding of amyloid beta has been shown to increase the aggregation of plaque in rodents; this has been reported in multiple mouse models of Alzheimer's disease (AD). However, the behavioural effects of the seeding have not been reported. This study aimed to investigate the effects of amyloid beta seeding on Morris water task (MWT) behaviour in the single APP knock-in mouse model (APPNL-G-F). The medial entorhinal cortex was injected with a homogenate of brain tissue from fast-spreading AD patients (FAH) or a control homogenate (CH) at two months of age. At three and six months, MWT was completed. At three months, the FAH and CH groups showed no impairment in performance. At six months the FAH group showed robust expression of plaque with 4G8 and GFAP staining; the CH group showed relatively minimal expression of amyloid plaque. At six months no difference in MWT performance between groups was found. Both groups showed deficits in performance. A secondary point of interest, which is under investigation, is the use of APPNL mice as a control for the APPNL-G-F mouse model. At three months the APPNL mice showed slight impairment, regardless of homogenate group, comparable to the APPNL-G-F group. At six months, the APPNL mice showed equal impairment when compared to the APPNL-G-F mice. These findings suggest amyloid plaque expression

does not correlate with spatial memory performance but perhaps other earlier steps in pathogenesis are responsible for cognitive deficits.

1-F-123 Electroencephalographic correlates for risk and ambiguity in financial decision making

Mitchel Kappen[1], Cameron Hassall[1], Olav Krigolson[1]

[1]University of Victoria

Our lives are filled with decisions, and rarely all potential outcomes of these decisions are known. Furthermore, we are constantly taking different levels of risk and ambiguity into account when we make decisions. Here we used electroencephalography (EEG) to examine how risk and ambiguity impacted reward processing during performance of a gambling choice task. However, unlike previous EEG studies focused on the examination of reward feedback (i.e., the feedback-related negativity/reward positivity) here we sought to examine the neural response evoked by the presentation of risky and ambiguous gambling choices. In line with previous work, our behavioural data show characteristic performance reflective of loss aversion. Interestingly, an analysis of our electroencephalographic (EEG) data demonstrated that varying levels of risk and ambiguity are differently represented in the brain. More specifically, we found that high risk and ambiguous gambles were associated with greater frontal theta activity than low risk and certain gambles. These results are in line with previous accounts that posits that increased frontal theta is associated with increased cognitive control (e.g., Cavanagh and Frank, 2014). We also found increased parietal alpha for low risk and certain gambles. This result is in line with accounts relating parietal alpha to the allocation of visuo-spatial attention (e.g., Klimesch, 2012).

1-F-124 Optogenetic activation of foraging neurons in Drosophila melanogaster induces a nociceptive-like escape behaviour

Jeffrey Dason[1], Amanda Cheung[2], Aaron Allen[3], Marla Sokolowski[3]

[1]University of Windsor, [2]University of British Columbia, [3]University of Toronto

The Drosophila foraging (for) gene has complex gene structure that contains four promoters (pr) and encodes a cGMP-dependent protein kinase. for regulates a number of behaviours however, little is known about the neural circuitry underlying these behaviours. We took an optogenetic

approach and activated subsets of cells that are associated with each of the four for promoters. We found that activation of for pr 1 cells resulted in a rolling behaviour that was reminiscent of a nociceptive-like escape response that is seen when Drosophila larvae are touched by a heated probe. To determine if for is involved in nociception, we tested a for null mutant for impairments in a thermal nociception assay. We found for null mutants displayed impaired responses to thermal nociception. These impairments were rescued by expressing for in pr1 cells of the for null. Knockdown of for in pr1 cells phenocopied the for null mutant. To gain insight into the circuitry underlying this rolling response, we used optogenetics to activate pr1 cells in conjunction with an intersectional approach and found that pr1 neurons in the ventral nerve cord were required for this rolling response. We then used activity-dependent GRASP to show that multidendritic sensory neurons, known to be required for the nociceptive-like escape behaviour, synapse onto pr1 neurons in the ventral nerve cord. Overall, our data demonstrates that for in the ventral nerve cord is required for a nociceptive-like escape behaviour.

1-F-125 Role for estrogen signalling in anxiodepressive behaviour induced by saturated high-fat feeding

Léa Décarie-Spain[1], Cécile Hryhorczuk[2], Alexandre Fisette[1], Élizabeth Jacob-Brassard[2], Thierry Alquier[3], Stephanie Fulton[1]

[1]CRCHUM - Univeristé de Montréal, [2]CRCHUM, UdeM, [3]Centre de recherche du CHUM

Obesity with metabolic dysfunction increases the risk for depression. The nucleus accumbens (NAc) is a brain region involved in goal-oriented behaviour, reward and hedonic impairments associated with mood disorders. Our group has recently demonstrated that a saturated, but not monounsaturated, high-fat diet (HFD) promotes anxiodepressive behaviour via NAc inflammation in male mice. As depression diagnosis is near double in women as compared to men, we set out to investigate the metabolic and behavioural outcomes of saturated and monounsaturated HFDs in female mice as well as to verify the relative contribution of NAc inflammation. Adult C57Bl6 female mice fed either a low-fat diet (17%kcal lipids; soybean oil), a saturated HFD (50%; palm oil) or a monounsaturated HFD (50%; olive oil) for 24 weeks (n=12/diet) were assessed in the elevated-plus maze and forced swim test. NAc gene expression for inflammation and estrogen receptors (ER) was determined by RT-qPCR. Plasma 17ß-estradiol was quantified by ELISA. Only mice fed the saturated HFD displayed increased anxiodepressive behaviour compared to controls. However inflammatory levels in the NAc did not differ between both HFDs. In fact, increased NAc ERα gene expression, as well as heightened 17β-estradiol

plasma concentrations, were associated with the anxiodepressive phenotype. This data suggests a saturated, but not monounsaturated, HFD elicits alterations in estrogen signaling that can contribute to anxiodepressive behavior and highlights a sexual dimorphism in the mechanisms underlying depression comorbid to obesity.

1-F-126 When a rat's past dictates its future: Effects of past activity-based anorexia on future cocaine self-administration

Stephanie Gallant[1], Michelle Da Paz[1], Nora Chujunian[1], Alexandra Usypchuk[1], Alexandra Chisholm[1], Uri Shalev[1]

[1]Concordia University

Anorexia nervosa (AN) is characterized by distorted body image, severe caloric restriction, and hyperactivity interfering with weight gain. AN is commonly associated with use and abuse of drugs such as cocaine. While many studies have examined the mechanisms involved in cocaine self-administration in rats, no study has explored cocaine self-administration in an animal model of AN-like behaviours. In activity-based anorexia (ABA), food restriction is combined with unlimited access to running wheels, resulting in hyperactivity and accelerated weight loss akin to that observed in AN. The goal of this study was to investigate whether rats with a history of ABA would show higher cocaine self-administration, seeking, and cue-induced reinstatement compared to sedentary controls. Female Sprague-Dawley rats were housed with continuous access to running wheels (ABA rats) or locked wheels (sedentary rats). Rats underwent two periods of 23 h/day food restriction (7-9 days) followed by a recovery period. Rats were then implanted with intravenous catheters and trained to self-administer cocaine, followed by a period of forced abstinence, extinction, and a cue-induced reinstatement test. Rats with a history of ABA, compared to sedentary rats, were more motivated to work for cocaine and showed greater resistance to extinction. Furthermore, rats that were most vulnerable to ABA (i.e., highest wheel running during food restriction) were most resistant to extinction. These results provide a novel approach to studying the overlapping mechanisms involved in co-occurring AN and substance use.

1-F-127 Morphometric Analysis of Dorsal Hippocampal 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 (sporadic) Alzheimer`s Disease (LOAD) has been hindered by the lack of animal models. Oxidative stress is a causative factor in LOAD, and we have developed an oxidative stress-based model of age-related cognitive impairment based on gene deletion of aldehyde dehydrogenase 2 (Aldh2), an enzyme important for the detoxification of endogenous aldehydes arising from lipid peroxidation. These mice exhibit a progressive decline in recognition and spatial memory, decreased hippocampal volume, and a number of AD-like pathological changes. In the current study, we performed morphometric analyses in the hippocampal CA1 region to determine whether altered neuronal structure might account for the observed cognitive impairment and hippocampal volume loss. Dendritic morphology of one year old mice was quantitatively analyzed following Golgi-Cox staining using 9 wildtype (WT) mice (37 neurons) and 15 Aldh2 null mice (60 neurons). Four to 6 pyramidal neurons were traced per mouse, followed by branched structured analysis and Sholl analysis of dorsal hippocampal CA1 pyramidal neurons. Our evaluation of neuronal morphology and complexity of neurons from Aldh2 null mice showed significant reductions in apical and basal dendritic length, and a reduction in the number of dendrite intersections, ends, and nodes, compared to WT controls. These findings indicate that CA1 dendritic complexity is significantly reduced in Aldh2 null mice, and suggest a structural basis for the cognitive deficits and reduced hippocampal volume seen in this LOAD model.

1-F-128 L-dopa impairs regularity detection: an auditory EEG study in pd and age-matched controls

Penny MacDonald[1], Jessica Grahn[1], Abdullah Al Jaja[2], Björn Herrmann[2]

[1]Western University, [2]Brain and Mind Institute/ Western University

Parkinson's disease (PD) is a common neurodegenerative disorder. In addition to motor symptoms such as bradykinesia, resting tremor, and rigidity, PD exhibits a number cognitive impairment. L-3,4-dihydroxyphenylalanine (L-Dopa) is the standard treatment of motor symptoms in PD. However, L-Dopa can adversely impact non-motor symptoms including aspects of cognition. Regularity detection (i.e., detection of regular patterns that emerge from a noisy scene) is an important innate response that permits navigation of complex visual and auditory environments. At the neural level, regularity detection manifests by the sustained

response, an evoked neural response that corresponds to ongoing presentation of the predictable, detected pattern. The effect of PD and L-Dopa on regularity detection is unknown. Toward increasing this understanding, we investigated regularity detection in PD patients and age-matched, healthy controls (HC) both on and off L-Dopa, measuring electroencephalographic (EEG) signal during presentation of two auditory stimuli. We recorded EEG signals in18 PD patients and 14 HC while they listened to Random (Rand) versus Regular (Reg) stimuli. In the OFF state, both PD and HC evidenced comparable sustained EEG responses in the Reg relative to Rand condition. We found that dopaminergic medication significantly impaired the sustained response in PD patients and HC, suggesting that L-Dopa compromises regularity detection. The mechanism for this effect and how it potentially relates to learning deficits that arise prominently as a result of L-Dopa in PD are discussed.

1-F-129 Neonatal Ventral Hippocampal Lesions (NVHL) rats show working memory deficits on a delayed alternation task

Nathaniel Powell[1], Jeremy Seamans[1]

[1]University of British Columbia

Neonatal Ventral Hippocampal Lesioned (NVHL) rats have been used as a model of the cognitive deficits in schizophrenia for many years. As a result of inappropriate connectivity during adolescence, NVHL animals show signs of a disinhibited prefrontal cortex in adulthood. Previous studies have found that NVHL rats have deficits in executive functions including working memory and set shifting. We analyzed in detail the behavior and Anterior Cingulate Cortex (ACC) recordings from a set of NVHL rats (Male, Long Evans) on a delayed alternation lever press task in an operant environment, with varying delay lengths. Both lesioned and sham-lesioned animals were highly accurate at this task when delays were less than 10 seconds, and both were correct around 50% of the time (chance) at delays longer than 20 seconds. However, the NVHL animals were much less accurate at intermediate delays of 10-20 seconds. Neurons recorded in the ACC of these animals showed more distinguishable representations of the left and right lever locations in the sham animals than NVHL animals, and this representational distinction was directly proportional to the animal's working memory performance on the task. Further, we found that this difference in PFC representational accuracy between groups does not appear to be due to increased noise in the cortex of NVHL animals, but rather differences in the underlying representations. Additionally, we found that NVHL animals appeared to be

employing an embodied cognition mnemonic strategy, although this strategy did not help their performance on the task.

1-F-130 The role of neurotensin in the bed nucleus of the stria terminalis in the augmentation of heroin seeking induced by chronic food restriction

Alexandra Chisholm[1], Rosalie Dauth[1], Emilie Fortin[1], Damaris Rizzo[1], Natasha Gonzalez[1], Alexandra Bumbu[1], Christina McAnulty[1], Shalev Uri[1]

[1]Concordia University

Our laboratory has demonstrated a robust increase in drug seeking following a period of withdrawal in chronically food-restricted rats compared to sated rats. However, the neural mechanisms that mediate this effect have not been elucidated. Neurotensin within the bed nucleus of the stria terminalis (BNST) has been associated with the effects of chronic stress. The objective of the current study was to study the role of neurotensin transmission within the BNST in heroin seeking under food restriction conditions. In experiment 1, rats were trained to self-administer heroin over a 10-day period. Following training, rats were removed from the operant conditioning chambers for a 15-day withdrawal phase. Over the withdrawal period, rats were exposed to a mild food restriction or were given unrestricted access to food. On the 14th of the withdrawal period, the neurotensin receptor antagonist SR 142948 (2 or 4 ng) or vehicle, was injected into the BNST before the heroin-seeking test. Experiment 2 was designed to replicate experiment 1 with an injection of SR 142948 (4 ng) or vehicle into the BNST. As expected, food-restricted rats demonstrated an augmented heroin seeking during the heroin-seeking test in comparison to sated rats. Unexpectedly, in the food restricted rats, blockage of neurotensin receptors in the BNST at both doses increased heroin seeking, although this effect did not reach statistical significance. These results suggest that neurotensin within the BNST may be involved in the augmentation of heroin seeking following chronic food restriction.

1-F-131 Neural Correlates of Feedback Congruency: Top-Down Modulation of the Reward Positivity

Taryn Berman[1], Ashley Howse[1], Chad Williams[1], Olav Krigolson[1]

[1]University of Victoria

Our efforts to process stimuli are impacted by a range of factors. For example, in previous work Krigolson and colleagues (2014) showed that cognitive load reduced the amplitude of the reward positivity, a component of the human event-related brain potential (ERP) that indexes reward processing. Here, we sought to examine the impact of feedback congruency - the conflict between the physical presentation of feedback stimuli and their actual underlying meaning. Participants performed a computerized task wherein they selected one of two colored boxes in order to win gambles while electroencephalographic (EEG) data was recorded. In a key manipulation, on half of the experimental trials the feedback was congruent - the physical presentation and meaning of the stimuli aligned whereas on the other half of the experimental trials the feedback was incongruent. For example, a check mark that indicated a loss is an example of an incongruent feedback stimuli. Analysis of the ERP data revealed that the reward positivity in the congruent condition had timing and scalp topography in accordance with previous literature. Intriguingly, we found a that the reward positivity had a reduced amplitude in the incongruent condition. We attribute this reduction in the reward positivity to a top-down bias modulating the amplitude of the component. These findings demonstrate that stimulus conflict and uncertainty have an observable effect on the reward positivity, and that the neural learning system may be modulated by top-down biases.

1-F-132 Glucocorticoid receptor phosphorylation in the dorsal and ventral hippocampus after acquisition of contextual fear conditioning

Renata Ponce Lina[1], Norma Serafín[1], Martha Carranza[1], Carlos Arámburo[1], Roberto Prado Alcalá[1], Maricela Luna Muñoz[1], Gina Quirarte[1]

[1]Instituto de Neurobiología, UNAM Campus Juriquilla

Glucocorticoid release during learning facilitates fear conditioning memory consolidation. This effect depends, among other factors, on glucocorticoid receptor (GR) activation. The GR is a transcriptional factor whose transcriptional activity and cellular localization depends on its phosphorylation. We investigated the effect of contextual fear conditioning (CFC) training on the phosphorylation of GR at serine 232 (Ser232) and serine 246 (Ser246) in dorsal and ventral hippocampus. Male Wistar rats were trained in CFC in a single session with different foot-shock intensities (0.0, 0.5, or 1.5 mA). Half the animals were tested for retention at 48 h post-training, and the other half was sacrificed 1 h post-training. We quantified the number of immunoreactive cells to total GR and GR phosphorylated at Ser232 or Ser246 in dorsal and ventral CA1, CA2, CA3 and the dental gyrus (DG) subregions. Rats trained with 0.5 and 1.5 mA

learned the task. CFC did not affect the number of cells expressing total GR. Regarding the two phosphorylated variants of the GR, we only found an increase of phosphorylated Ser246 immunoreactivity in ventral CA1 and DG. These results indicate that during the acquisition phase of CFC, GR phosphorylation in Ser246 in ventral CA1 and DG, is one of the molecular processes by which glucocorticoids enhance fear memory consolidation. We acknowledge the assistance of B. Islas, C. Medina, M. García, L. Casanova, O. González, S. Hernández, and L. Lara. Funded by CONACYT (251634, 285004, Scholarship to RPL 342154) and PAPIIT-UNAM IN204118, IN201817 and IN207018.

1-F-133 Effects of Centrally and Systemically Administered Thiamethoxam on Central Nervous System Function in the Rat

Maria Soriani[1], Jerrica Cormier[1], Andrew Tasker[1]

[1]University of Prince Edward Island

Over the last decade, the agricultural and veterinary use of neonicotinoids has increased faster than any other class of pesticides. Neonicotinoids are acetylcholine agonists that have a higher affinity for the nicotinic acetylcholine receptors (nAChRs) found at the neuromuscular junction of insects than vertebrate species and are therefore, considered safe for widespread applications. However, recent studies have shown that neonicotinoids can cause sub-lethal effects on fishes, birds and even small mammals, and their affinity for nAChR subtypes found in the mammalian CNS is unknown. To explore potential CNS effects in mammals we administered low doses of the neonicotinoid thiamethoxam (or vehicle controls) both i.c.v. and i.p in groups (n=8) of male CD rats followed by testing in horizontal ladder, novel object and spontaneous alternation tasks. Following testing rats were euthanized and the brain sectioned to confirm cannula placement in the lateral ventricle for i.c.v. groups, and sections from the cortex and hippocampus were examined histologically using both hematoxylin-eosin staining and immunohistochemistry for signs of cellular damage. Results to date indicate no significant differences in either behavior or histopathology between treated and control rats with either route of administration. Funding provided by NSERC

1-F-134 Neuroplasticity modulation by 4E-BP1 protein during motor skill learning

Maxence Brouillette[1], Michel Cyr[2]

[1]UQTR - Université du Québec à Trois-Rivières, [2]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. The present study has explored the role of two well-established mTOR substrate, the ribosomal protein S6 kinase beta-1 (P70S6K) and 4E binding proteins (4E-BP1), 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. Western blot analysis in the striatum structure of these mice revealed that levels of P70S6K were unaffected during rotarod training. By contrast, phosphorylated 4E-BP1 was decreased on day 1, 2 and 3 when compared to untrained mice (control). Interestingly, these levels were equal to control values on day 4 and 8, suggesting that 4E-BP1 phosphorylation status goes back to its original state once the rotarod task is learned. These findings propose that a diminution of phosphorylated 4E-BP1 in the striatum of mice is associated with motor learning rather than motor execution, whereas P70S6K activity is not implicated.

1-F-135 Behavioural phenotypes associated with the MDGA2+/- mouse model of Autism spectrum disorder

Richard Brown[1], Michaela Purdon[1], Emre Fertan[1]

[1]Dalhousie University

Autism Spectrum Disorder (ASD) is a developmental disorder characterized by numerous behavioural symptoms, the most pervasive being restricted and repetitive behaviours, inhibited communication, and reduced sociability. A MAM domain-containing glycosylphosphatidylinositol anchor 2 (MDGA2) gene has been linked to ASD in humans (Bucan M. et al., 2009, PLOS. 5:6). Connor S. A. et al. [2016, Biological Psychiatry. 64: 583-8] showed that haploinsufficency at MDGA2 in the MDGA2+/- mouse model resulted in behavioural phenotypes which parallel those seen in humans with ASD, including stereotypy, social interaction deficits, and altered cognition. The MDGA2+/- mouse model used by Connor et al. (2016) was bred using a C57BL/6N background strain, which has a retinal degeneration 8 mutation that causes retinal spotting. Our study used two-month old transgenic (MDGA2+/-)

mice and wildtype (MDGA2+/+) littermate controls which were bred using a C57BL/6J background which does not have retinal degeneration. These mice were tested for visual ability using OptoMotry in order to ascertain whether visual impairment may have been a confounding variable in the Connor et al. (2016) study. Behavioural phenotyping was done with a test battery that included the open field, novel object recognition, balance beam, Rotarod, social affiliation test, three chamber social interaction, Morris water maze, and contextual fear conditioning. Results indicate some genotype and sex differences, which will be described in detail and compared with the findings of Connor et al. (2016).

1-F-136 Optogenetic silencing of activity in the prelimbic cortex during action selection and action outcomes differentially biases risky choice

Debra Bercovici[1], Oren Princz-Lebel[1], Stan Floresco[1]

[1]University of British Columbia

Decision-making often requires us to weigh costs and benefits associated with different options that vary in terms of reward magnitude and uncertainty. We have previously shown that the prelimbic cortex (PL) plays a key role in updating behaviour to changes in reward contingencies and biases choice towards more profitable options when the probability of reward delivery shifts. However, how choices are shaped by activity in the PL, occurring prior to choices or when their outcomes are realized, is unknown. Using optogenetics, we assessed how temporally-specific phasic neural activity within the PL during different phases of the decision process influences choice. Rats received intra-PL infusions of AAV encoding the inhibitory opsin eArchT and were well-trained on a probabilistic discounting task, where they chose between a smaller/certain reward and a larger reward delivered in a probabilistic manner, with the odds of obtaining the larger reward changing over a session (50-12.5%). During testing, discrete ~5 s pulses of light were delivered via optic fibers into the PL to suppress activity during specific task events; during periods "prior to choice" or after different "choice outcomes". Preliminary results suggest that suppressing PL activity prior to choice alters choice behaviour differently from activity during choice outcomes. These findings provide novel insight into how discrete patterns of firing within the PL convey contrasting types of information that guide flexible decision making in situations involving reward uncertainty.

1-F-137 The medial orbitofrontal cortex plays a dissociable role in "reinstater" vs "non-reinstater" rats during cue-induced reinstatement of reward-seeking behaviour

Nicole Jenni[1], Nicola Symonds[1], Stan Floresco[1]

[1]University of British Columbia

The understudied medial subregion of the orbitofrontal cortex (mOFC) plays an important role in value-based decision-making, but its role in mediating relapse, or the reinstatement of reward seeking behaviour, is not yet fully understood. The present study examines the role of the mOFC in cue-induced reinstatement of reward-seeking behaviour. Rats were trained to lever press for a sucrose reward, contingent with the delivery of a tone and light cue. They then underwent extinction, followed by a reinstatement test where lever presses produced the reward-paired cues alone. The ability for this Pavlovian cue to invigorate instrumental reward-seeking, indexed by the number of lever presses, was measured following intra-mOFC infusions of either saline or GABA agonists (to temporarily inactivate neural activity). mOFC inactivation induced differential effects on cue-induced reinstatement of reward-seeking that were dependent upon baseline performance. "Reinstater" rats that displayed robust responding under control conditions showed no reinstatement after mOFC inactivation. In contrast, for "non-reinstater" rats that showed little responding under control conditions, mOFC inactivation robustly increased reinstatement. These data suggest that baseline differences in reinstatement may be supported by differences in mOFC encoding of expected value during the extinction phase of the task. These findings have important implications for understanding the circuitry that drives pathological patterns of reward seeking in individuals with substance use or behavioural disorders.

1-F-138 Great, I found it: Evidence for the association of reward with spatial information following navigation with the use of EEG

Thomas Ferguson[1], Chad Williams[2], Ron Skelton[2], Olav Krigolson[2]

[1]Center for Biomedical Research, University of Victoria, [2]University of Victoria

In navigational research, a long running debate has been whether or not spatial navigation is a unique form of learning. Although much of the debate has focused on whether or not the cognitive map automatically updates, other research has instead focused on whether the creation of a cognitive map involves the reward system. While not entirely confirmed, some research has found evidence of a role of the reward system during navigation. The present

experiment attempted to further investigate this claim through the use of EEG following navigation in a multi-strategy radial arm maze (the Hex-maze). Following strategy acquisition in the Hex-Maze, participants were presented with images corresponding to the information they used during navigation. The present experiment sought to determine if navigators learned the information they had used to navigate in a rewarding manner. The results showed that navigators who used a cognitive map-based strategy had a different neural response when comparing positive navigational information (information that helped them find the platform), to negative navigational information (information that did not help them find the platform). Thus, the present results do suggest a further role of the reward system in cognitive map creation, and thus that the relationship between spatial learning and learning in general may merit further examination.

1-F-139 Relationship between Response Network and Default Mode Network Predicts Reaction Time in the Stroop Task Paradigm

Jessica Luk[1], Todd Woodward[1]

[1]University of British Columbia

Schizophrenia has been consistently shown to be related to disrupted functional neural networks, yet few studies to date have investigated the relationships between networks. In the current study, 13 participants with schizophrenia and 13 healthy controls completed a task-switching version of the Stroop paradigm in a functional magnetic resonance imaging (fMRI) scanner. Imaging data was analyzed using fMRI-constrained principal component analysis, which allows extraction of independent sources of coordinated brain activity during a task period. This revealed two networks: a primary response network (RN) and the default mode network (DMN). A hemodynamic response (HDR) curve, indexing the functional activity of each network was extracted, and was then further submitted to a principal component analysis to investigate interrelationships existing between networks. The first of two components showed the end of the RN as being negatively correlated with the peak activity of the DMN, and correlated with the beginning and end of the DMN HDR. The second component revealed that the peak of the RN activity negatively correlated with the off-peak of the same network. Importantly, the first component showed a significant negative correlation with reaction time in the colour incongruent condition ($r = -0.66$, $p < 0.02$). Moreover, this correlation was seen in the healthy group only, with a significant difference in correlations between groups ($p < 0.01$). These

findings underline the importance of investigating not only within a functional network, but also between neural networks.

1-G-140 High-density lipoproteins reduce amyloid-beta-deposition in a novel in vitro model of the human brain vasculature

Jerome Robert[1]

[1]University of British Columbia

Amyloid plaques, consisting of deposited beta-amyloid (Aβ), are a neuropathological hallmark of Alzheimer's Disease (AD). Cerebral vessels play a major role in AD, as Aβ is cleared from the brain by pathways involving the cerebrovasculature, most AD patients have cerebrovascular amyloid (cerebral amyloid angiopathy (CAA), and cardiovascular risk factors increase dementia risk. Here we present a notable advance in vascular tissue engineering by generating the first functional 3D model of CAA in bioengineered human vessels composed of endothelial and smooth muscle cells without or with astrocytes. We show that lipoproteins including brain (apoE) and circulating (high-density lipoprotein, HDL) synergize to facilitate Aβ transport across bioengineered human cerebral vessels. Moreover, apoE4 is less effective than apoE2 in promoting Aβ transport, also consistent with the well-established role of apoE4 in Aβ deposition in AD. Taken together, our results establish the utility of human engineered cerebral vessels as highly innovative in vitro platform to study key mechanistic questions relevant to lipoprotein and AD.

1-G-141 Machine learning classification of children with Fetal Alcohol Spectrum Disorder through eye movement behaviour analysis

Deng Wang[1], Shelby Thompson[1], Kennedy Denys[2], Katherine Flannigan[2], Gunnar Blohm[1], Tim Oberlander[2], Christine Loock[2], James Reynolds[1]

[1]Queen's University, [2]University of British Columbia

Background: Diagnosis of FASD can be a lengthy process frequently involving long wait times. New screening tools that can provide objective assessments of brain dysfunction could streamline the process. Deficits in eye movement control have been shown to differentiate children with FASD from typically developing controls. Aims: To utilize functional biomarkers

from eye movement control tasks to build and test a classifier that can accurately identify children with FASD. Methods: A large sample of individuals with FASD (N=95) and age-matched healthy controls (N=115) performed three eye movement tasks (pro-saccade, anti-saccade and memory-guided saccade) that assess automatic and voluntary responses, spatial working memory, and visuospatial abilities. An analytics pipeline that included Fisher feature selection and Gaussian Naive Bayes classifier was built to discriminate between children with a FASD and controls. Results: Using feature selection, 19/216 outcome measures from the 3 tasks produced optimal performance of the classifier, with features from all 3 tasks contributing to performance. Overall accuracy was 79%, with good sensitivity (78%) and specificity (80%). Outcome measures that contributed most to the performance of the classifier all exhibited large effect sizes and significant group differences at the 99% confidence level. Conclusions: Machine learning-based algorithms and data-driven modelling of eye movement control presents an opportunity to exploit functional biomarkers of FASD that can contribute to rapid, low-cost and high-throughput assessment protocols.

1-G-142 MiniSOG photoconversion as a new tool to study the ultrastructural features of cholinergic axons in the subthalamic nucleus

Maya Chebl[1], Cynthia Lecours[2], Christophe Proulx[1], Marie-Eve Tremblay[2], Martin Parent[3]

[1]Centre de recherche CERVO, [2]Centre de recherche du CHU de Québec, [3]Université Laval

Electron microscopy (EM) remains the best methodological approach to precisely describe the fine morphological features of synapses. In order to characterize subgroups of neuronal elements, most researchers rely on immunohistochemistry with the inherent constraint imposed by a limited penetration of antibodies, thus precluding three-dimensional reconstructions of neuronal elements through large volumes of brain tissue. In this study, we used a fluorescent protein called mini singlet-oxygen generator (miniSOG). Under blue light illumination, the expression of this protein leads to the precipitation of a chromogen (DAB) that can readily be detected by EM. Targeted expression of miniSOG in cholinergic neurons using ChAT-cre mice and intracerebral stereotactic injections of viral vectors in the pedunculopontine nucleus (PPN) has helped us to provide new data on the ultrastructural and relational features of cholinergic axons in the subthalamic nucleus (STN). Our method provides a strong expression of miniSOG in the entire axonal arborization of cholinergic neurons. In addition, the lack of reagents in the preparation helps to preserve tissue integrity. This new technique is now being exploited to produce three-dimensional reconstructions of cholinergic axonal segments in the STN and cell

bodies in the PPN. The extensive characterization of their fine morphological and ultrastructural features is made possible with the use of focussed ion beam scanning electron microscopy (FIB-SEM).

1-G-143 Portable Electroencephalography: Investigating Self-Reported Fatigue and the P300

Wande Abimbola[1], Olav Krigolson[2]

[1]Centre for Biomedical Research, University of Victoria, [2]University of Victoria

In recent years, there has been a notable proliferation of portable electroencephalographic systems (EEGs) available for use by both the public and researchers. However the use of these systems has not matched their increased availability, and their compact design has not been taken advantage of by researchers for studies in the field, or to expand the pool of individuals event-related-brain potential (ERP) studies are conducted on. In this study we conducted ERP research using a MUSE EEG system and phone application (PEER) and report the results of an experiment using the visual-oddball paradigm to examine the relationship between fatigue and the amplitude of the P300 ERP component. Combining the PEER application and the MUSE, we were able to identify and quantify the P300 component resulting from engagement with the oddball task, and correlate acquired P300 components with participants self-reported fatigue. A negative correlation was found between self-reported fatigue and P300 amplitude, placing our results in line with the existing literature. The work reported here was founded on a simple methodology, however it serves to highlight the ease with which ERP studies may be conducted, and shows there is potential for an expansion of ERP research into previously under-examined participant groups and new contexts.

1-G-144 Rapid optogenetic kindling in neocortex

Amanda McFarlan[1], Amrit Sampalli[1], Elvis Cela[1], P. Jesper Sjöström[1]

[1]McGill University Health Centre

Efforts to study the underlying mechanisms of epileptogenesis - the gradual process by which a healthy brain develops epilepsy - have been accomplished through the development of animal models of epilepsy. We have previously developed an optogenetic kindling model of epilepsy to

investigate how cortical circuits are altered during epileptogenesis. One drawback of our model was that it required up to two months to complete. To overcome this limitation, we have modified our protocol to generate a rapid optogenetic kindling model that can be carried out in one week. For our rapid kindling model, we used bilateral stereotaxic injection of AAV-CaMKIIα-hChR2-E123T/T159C-p2A-EYFP to express Channelrhodopsin-2 in pyramidal cells of mouse primary motor cortex. Next, we stimulated awake behaving mice every 24-48 hours with fiber-coupled 445-nm lasers while recording video and EEG. Animals were stimulated using either a theta frequency (n=4) or delta frequency (n=4) protocol. The delta frequency protocol yielded seizures over five sessions in one week in three of four mice, while the theta frequency protocol yielded seizures in four out of four mice. Additionally, we observed two of the four classic markers of kindling: seizure threshold decreased while the behavioural seizure score increased, indicating that seizures worsened over the five sessions. Seizure duration and seizure frequency, however, were unaltered. With our rapid kindling protocol, we can evoke seizures in only five stimulation sessions. We are currently further refining the protocol to optimize our model.

1-G-145 Optogenetic strategy to measure chloride transport kinetics in single neurons in situ

Isabel Plasencia Fernandez[1], Yves De Koninck[1]

[1]Université Laval - CERVO Research center

Chloride (Cl-) homeostasis is crucial to maintain proper inhibition in the CNS. The K+-Cl- cotransporter KCC2 is a key protein for controlling Cl- balance in mature neurons and deficits in KCC2 function appears involved in several CNS pathologies. Because it is electroneutral, it has remained a challenge to measure KCC2 function in neurons. Measuring anion reversal under a Cl- load, with high intrapipette Cl- during patch-clamp recordings, has been used to estimate Cl- extrusion capacity in cells. But this approach lacks temporal resolution, since measurements are under steady state conditions. A strong Cl- load may also trigger adaptive changes in cells. Cl- imaging has also been used, measuring changes in [Cl-]i upon abrupt changes in [K+]o to modify the rate or direction of KCC2 transport. Yet, the latter yields insufficient temporal resolution to measure fast transport dynamics. An alternative is to measure the recovery of responses to GABA applications after a sudden Cl- load. The approach relies on GABAA receptor function though and it remains challenging to measure fast kinetics. To fill this gap, we developed an optogenetic approach, using NpHR, a light-driven inwardly directed Cl- pump to achieve fast, transient Cl- load in neurons, combined with measuring Cl- currents through iC++,

a light-gated Cl- permeable opsin. The time for recovery to full outward current through iC++ revealed the rate of Cl- transport, independent of endogenous Cl- conductance. The fast kinetics of iC++ allowed us to resolve fast kinetic changes in Cl- transport induced by KCC2 modulators.

1-G-146 Ligand-directed integrin labeling: Novel insights into glia mediated engulfment in synaptic elimination

Wyatt Slattery[1], Fred Menard[1]

[1]University of British Columbia Okanagan

Integrins (ITGs) are transmembrane receptors that mediate cellular adhesion to the extracellular matrix and initiate diverse signaling cascades. The ITG alphaV beta5 (αVβ5) heterodimer participates in engulfment processes and is enriched in glial cells of the central nervous system. Engulfment processes mediated by ITG αVβ5 in the brain may be involved in synaptic elimination events occurring in neurodegenerative disease. Preliminary findings in M1 phenotype microglia in vitro demonstrate that the ITG αVβ5 inhibitor, cilengitide, attenuates phagocytic activity. Since ITG αVβ5 heterodimers involved in engulfment processes exhibit a unique subcellular localization relative to ITG heterodimers that mediate cellular adhesion, real-time evaluation of ITG αVβ5 localization in vivo will help define the role of ITG αVβ5 in synaptic elimination. Current methods for fluorescently labeling endogenous proteins include immunostaining and the expression of recombinant fusion proteins; however, these methods are not rapidly applicable in live-cell systems. To address this, we have synthesized a chemical probe that fluorescently labels ITG αVβ5. This study reports the chemical structure and the pharmacodynamic properties of the probe, finding that it labels cells rapidly, binds specifically to ITG αVβ5, and maintains its potency following covalent modification with a fluorophore. The probe enables effective tracking of endogenous ITG αVβ5 in live-cell systems and is a critical first step towards understanding the role of integrin signaling in synaptic elimination.

1-G-147 Automated, high-throughput assessment of functional connectivity in mouse homecage following stroke

Matilde Balbi[1], Matthieu Vanni[1], Jamie Boyd[1], Federico Bolanos[1], Jeffrey LeDue[1], Timothy Murphy[1]

[1]University of British Columbia

Combining functional imaging with head-fixed behavioral assessment has become an important and powerful tool in systems neuroscience. Behavioral training of individual animals by experimenters has limiting factors that could be eliminated by automation. Here, we report a fully automated homecage-based system that identifies, weighs, head-fixes, and rewards mice for task participation. The system can house up to 10 mice for automated imaging during a forelimb motor task through a bilateral transcranial window. Mice pull a lever for a water reward upon receiving a somatosensory cue (0.1-0.2 sec pulse of a vibration motor attached to the chamber). Mice were trained to withhold licking the waterspout using feedback auditory cues. Using genetically encoded calcium indicator transgenic mice GCaMP6, we monitored cortical activity during task performance 24h a day for up to 90 days. To test the sensitivity of our system to changes in functional connectivity, we induced unilateral photothrombotic stroke on day 67. Despite having a stroke in an area between sensory and motor cortex-(1.5; 0.5) mm from bregma-mice were still able to perform high levels of head-fixed trials: 6 mice generated ~3h of head-fixed imaging data per day. Seed-pixel correlation maps revealed reductions in functional connectivity within 10 days after stroke, which recovered over the course of 2 weeks. Moreover, mice exhibited a lower count of motifs in areas adjacent the stroke. Our system will allow us to longitudinally assess functional connectivity and fine motor behaviors in health and disease such as stroke

1-IBRO-148 mechanisms underlying neuroprotection against Ischemia-like damage on differentiated neuroblastma SH-SY5Y cells

RACHID AKKI[1], Rosalba Siracusa[2], Rossana Morabito[2], Alessia Remigante[2], Michela campolo[2], Mohammed Errami[1], Giuseppina La Spada[3], Salvatore Cuzzocrea[3], Angela Marino[3]

[1]Faculty of Sciences, University Abdelmalek Essaadi, [2]University of Messina, [3]University of Messinaadi

Oxidative stress has long been implicated in the pathogenesis of various neurodegenerative disorders. While high levels of oxidative stress are generally associated with cell death, a slight rise of reactive oxygen species (ROS) can be protective by "preconditioning" cells. The aim of the present study was to verify whether and how neuronal?like differentiated SH-SY5Y cells may adapt to a mild and transient H2O2-induced oxidative stress. To this end, either 100 or 200 or 300 µM H2O2 were chosen to induce cell damage, while not necrotic H2O2 concentrations (10 to 50 µM) were chosen for PC protocol, consisting in pre-exposure to low-concentrated H2O2, followed by treatment with higher H2O2 concentrations (100 to 300). Cell viability measured 24

h after 100 μM H2O2-induced damage was significantly ameliorated when cells were pre-exposed to low concentrated-H2O2 for 24 h with cell size, as well recovered. Markers for apoptosis, inflammation and redox system were also determined, showing that, in preconditioned cells (pre-exposed to 10 μM H2O2 for 24 h and then damaged with 100 μM H2O2), Bcl-2 levels were higher, while Bad and iNOS levels were lower than those observed in damaged cells. MnSOD levels was unchanged under both damage and PC μM). Here we show that: i) apoptotic and inflammatory pathways are involved in such response, unlike antioxidant system, here represented by MnSOD, which, nonetheless, is worthy of further investigation; ii) an endogenous neuroprotective strategy of these cells may be suggested, giving a basis to shed more light on in vivo PC mechanisms.

1-IBRO-149 Neuronal glycoprotein m6a as a key regulator of synaptic plasticity during extra uterine brain development

Gabriela Aparicio[1], Micaela García[1], Alberto Frasch[1], Camila Scorticati[1]

[1]Instituto de Investigaciones Biotecnológicas Dr. Rodolfo Ugalde - Universidad Nacional de General Sa

Neuronal membrane glycoprotein M6a promotes neurite and axonal outgrowth, spines induction and synapse formation. The decreased of M6a levels in the cellular membrane affects both the synapses and the spines number. However, the modulation of M6a by potential ligands remains unknown. In humans, GPM6A gene variants have been related to schizophrenia, bipolar disorders and Alzheimer's disease. During the development, neurons change the number of dendritic spines and synapses in a process called pruning. Schizophrenia and Alzheimer's disease are closely related to this process. There is little evidence linking M6a to the development of the brain. Therefore, we aim to (1) identify potential ligands that interact with the external loops (ECL) of M6a and (2) to analyze the variation of M6a levels throughout brain development. For (1), we cloned and expressed the ECLs of M6a in HEK293 cells. Then, ECL-M6a was characterized by immunofluorescence, Dot blot and Western blot. For (2), brain samples from Sprague-Dawley rats at different stages of development were taken. M6a levels were quantified by Western blot at different growth stages. Our results indicate that M6a increases from P0 to P20 and remains constant until P90 in both hippocampus and prefrontal cortex. In contrast, an increase in M6a levels between P0 and P5 in the striatum was observed, followed by a decrease in its concentration up to P90. This result indicates that M6a plays a role during brain

development in postnatal stages. Also, this is the first time that is described the presence of M6a in the striatum.

1-IBRO-150 Investigating the epileptogenic potential of Taenia excretory/secretory products and acetylcholinesterases

Anja de Lange[1], Joseph Raimondo[1]

[1]University of Cape Town

Neurocysticercosis (NCC) is a medical condition in humans where larvae of the cestode Taenia solium infect the nervous system. Seizures are the most common symptom of NCC and these affect millions of people worldwide. Although the onset of symptoms in NCC has been linked to the death of larvae, the mechanisms underlying seizures remain unknown. To evade the immune system cestodes secrete various products. We set out to investigate the epileptogenicity of the excretory/secretory (E/S) products of Taenia larvae. We utilized Taenia crassiceps (T. crass) in conjunction with an ex vivo organotypic rat hippocampal brain slice model to investigate the effects of these products on neuronal and network excitability. Acute effects were assessed by puffing T. crass E/S products onto neurons on a patch clamp rig. Chronic effects were assessed using a co-culture model of T. crass larvae and hippocampal slices and network excitability was assessed on an interface rig. Taenia larvae and E/S products were assayed for acetylcholinesterases (AChEs), enzymes that are commonly secreted by cestodes and which could potentially impact on acetylcholine signaling in the brain in NCC. We show that Taenia E/S products appear to have an acute excitatory impact on neurons, but that chronically Taenia larvae do not alter seizure susceptibility. Further, we illustrate that Taenia larvae produce AChEs and that these appear to be active at the tegument surface. We conclude that there is a strong possibility that Taenia E/S products and AChEs may play a role in the changes in brain excitability seen in NCC.

1-IBRO-151 Entrainment of the circadian clock in the goat (Capra hircus) by daily ambient temperature cycles

Hicham Farsi[1], Driss Harti[1], Mohamed Rachid Achaaban[1], Mohammed Piro[1], Veronique Raverot[2], Beatrice Brothorel[3], Mohammed Ouassat[1], Etienne Challet[3], Paul Pevet[3], Khalid El Allali[1]

[1]Hassan II Institute of Agronomy and Veterinary Medicine, [2]Centre de Biologie Est - Groupement Hospitalier Est Hospices Civils de Lyon, [3]University of Strasbourg

In desert areas, species are exposed to harsh environmental conditions. It has been demonstrated for the first time, that the ambient temperature (Ta) cycles are able to entrain circadian biological clock in the mammal, the camel. In the present work, we assumed that in the goat, living in a desert, Ta cycles would have the same synchronization effect on the circadian biological clock, and therefore we studied its effect on body temperature (Tb), locomotor activity (LA) and melatonin rhythms as outputs of the circadian biological clock. The work was carried out on male goats kept first under constant conditions (continuous darkness (DD), constant Ta), then maintained under (DD), we applied Ta cycles mimicking the natural environment. Finally, we reversed the Ta cycles to get the peak heat overnight and low temperatures during the day. The results show that under constant conditions the rhythm of Tb and LA are endogenous with a circadian period of 25.5 and 25.0 respectively. Ta cycles entrain the rhythm of Tb and LA to a period of 24.0h and induce an acrophase respectively at, 03h41 pm and 02h18 pm. The reverse of Ta cycles induces an inversion of the rhythm of both Tb and LA: acrophases respectively at 01h04 am and 02h15 am. In the same way, the results shown that Ta cycles is able also to entrain melatonin rhythm, by reversing its phase. As in the camel, these results show that the Ta cycles are able to entrain the circadian biological clock in desert goat.

1-IBRO152 Evidence for progenitor cell reprogramming in the developing cerebral cortex following selective neuronal ablation

Bruna Landeira[1], Jéssica Araújo[1], Marcos Costa[1]

[1]Universidade Federal do Rio Grande do Norte - Instituto do Cérebro

During development, the cerebral cortex are sequentially established: deep-layer neurons are generated prior to upper-layer neurons. Notably, there is a good correlation among the generation time, laminar position and hodological features of neurons: i) Layer VI, corticothalamic neurons (CTN); ii) Layer V, corticofugal neurons (CFN); iii) Layer IV, stellate neurons; and iv) Mostly layers II-III and V, cortico-callosal neurons (CCN). In this study we report the influence from early-generated neurons to the generation of subsequent neuronal cohorts. We induced the selective cell death of early-generated CTN and CFN and fate-mapped the neuronal population generated after ablation. We observed that 24h after ablation, progenitor cells, which are usually committed to generate stellate neurons and CCN, resumed the generation of CTN. Interestingly, many of these neurons settled ectopically within layers II-III, as

expected for CCN neurons generated at the same stage, suggesting that migration of post-mitotic neurons is independent of cell-type specification. Using in vitro assays to further interrogate the mechanisms of progenitor cell re-specification following neuronal ablation, we found that only neuronal ablation in situ was capable of inducing the generation of CTN again. Moreover, we also observed that cell-cell communication plays an important role in the acquisition of unique neuronal phenotypes. Together, our data indicate the existence of feedback signals from early-generated neurons to progenitor cells and immature neurons controlling the generation of CCN.

2-A-1 Examining possible sex differences in maturation rate of new neurons in adult rats

Daria Tai[1], Shunya Yagi[1], Liisa A. Galea[1]

[1]University of British Columbia

Adult neurogenesis involves the production and maturation of neurons and is seen in the dentate gyrus of most mammals. Cognitive training upregulates hippocampal neurogenesis in male but not in female rats. However, activation and number of new neurons are more strongly associated with performance in females, thus it is plausible that the new neurons are more excitable or that the new neurons mature at a different rate in females compared to males. This study aims to determine whether there are sex differences in the components of neurogenesis including the ability to proliferate, the survival of new neurons, or maturation rate to become new neurons. Male and female rats received an injection of bromodeoxyuridine (BrdU) and were perfused 1, 2, or 3 weeks later. Immunohistochemistry was performed to visualize proliferating cells with Ki67, an endogenous protein expressed during all stages of cell-division cycle and new neurons by co-labelling for BrdU and neuronal nuclei (NeuN) or doublecortin (DCX), protein markers for mature and immature neurons respectively. Preliminary results suggest that while cell proliferation in the dentate gyrus is higher in males compared to females, the percentage of BrdU/DCX co-labeled cells is not significantly different between males and females in the dorsal dentate gyrus. Further analyses is currently undergoing. These findings will help determine whether there are sex differences in the maturation and timing of neurogenesis in the hippocampus of adult rodents.

2-A-2 Presynaptic development precedes dendritic input in C. elegans inhibitory motor neurons: different assembly sequences and a strategy to minimize disruption to circuit output

Ben Mulcahy[1], James Mitchell[2], Daniel Witvliet[1], WanXian Koh[1], Maggie Chang[1], Peter Bermant[2], Doug Holmyard[1], Richard Schalek[2], Jeff Lichtman[2], Andrew Chisholm[3], Aravinthan Samuel[2], Mei Zhen[1]

[1]Mount Sinai Hospital, [2]Harvard University, [3]UCSD

After birth, the human nervous system continues to develop. Existing circuitry undergoes remodelling, and neurogenesis generates new neurons that integrate into the neural ensemble. This has to occur with minimal disruption to circuit output. The cellular mechanisms facilitating this are unclear. To address this, we took advantage of the small nervous system of C. elegans. Over 1/4 of the C. elegans nervous system is born after hatching, and the motor circuit undergoes significant remodelling. After hatching, one class of GABAergic body motor neurons inhibits ventral muscles. Part way through development a second class is born and takes over the role of the first class, which in turn disassembles its synapses and switches polarity to inhibit dorsal muscles. Although the ultrastructure before and after remodelling has been described, observation of the intermediate stages could provide valuable information on the cellular mechanisms of circuit remodelling. We used electron microscopy to survey GABAergic motor neurons at successive stages of development. We observe interactions between embryonic and postembryonic structures, different sequences of presynaptic assembly, and the initiation of presynapse development prior to the appearance of dendritic input. Remodelling is temporally staggered across adjacent motor neurons. These observations suggest a strategy available to remodelling neural circuits, where neurons first develop their neurite morphology and presynaptic compartments, then send dendritic spines to integrate into existing circuitry.

2-A-3 Adult Neurogenesis Regulates the Activity of Neurons Born in Early Postnatal Development

Shaina Cahill[1], Angela Martinovic[1], John Darby Cole[1], Jason Snyder[1]

[1]University of British Columbia

The dentate gyrus (DG), a subregion of the hippocampus known for its role in learning and memory, is made up of two distinct populations: those added in adulthood and those born in development. We previously found that mature developmentally-born neurons die throughout

young adulthood, possibly to balance out the continued addition of adult-born neurons. Here, we hypothesized that activity in older, developmentally-born neurons depends on the numbers of adult-born neurons that are present. To test this, we either inhibited or enhanced adult neurogenesis and then quantified activity-dependent immediate-early gene expression in developmentally-born cells after rats explored a novel environment. Rats were injected with the mitotic marker BrdU at the peak of DG development and were given one of two treatment types in adulthood (2 to 6 months of age). To inhibit adult neurogenesis, a transgenic rat model (GFAP-TK) was used. We found that inhibition of adult neurogenesis increased activity in the developmentally-born cells. To increase adult neurogenesis, rats received a combined treatment of running and memantine. Increasing adult neurogenesis lead to compensatory decreases in activity of developmentally-born cells. We are currently examining overall patterns of activity to determine whether changes were specific to the developmentally-born population. Collectively, out data suggest that adult-born neurons inhibit developmentally-born neurons, thereby homeostatically regulating activity levels in the DG during learning.

2-A-4 Adult-born neurons modulate activity in developmentally-born neurons in the rodent dentate gyrus

Alyssa Ash[1], Jack Clemans-Gibbon[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 postnatal day 1 or 6 weeks of age to express the inhibitory DREADD receptor, HM4Di, in neurons born in early development or 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 and then trained in the water maze (8 trials). One hour after water maze training brains were collected and processed immunohistochemically for BrdU, GFP and c-Fos to identify neurons that were recruited during learning. We found that silencing a subset of adult-born neurons increased activity levels in the developmentally-born neuron population. Our novel findings

indicate there is a modulatory subcircuit between neurons of different ages within the DG, which has implications for the importance of adult neurogenesis in learning.

2-A-5 Regional distribution, density, and morphology of the peripheral myeloid cells invading the murine brain during normal postnatal development

micael Carrier[1], Julie Savage[2], Frederic Geissmann[1], Marie-Eve Tremblay[3]

[1]CHU de québec CHUL, [2]Université Laval, [3]Centre de recherche du CHU de Québec

Microglia are the resident immune cells of the brain that exclusively derive from the embryonic yolk sac. During trauma or disease, bone marrow-derived cells (BMDC) can also invade the brain, infiltrating through the blood-brain barrier (BBB), to accomplish neuroinflammatory roles. We have described at the ultrastructural level a new phenotype of brain myeloid cells that is highly prevalent upon chronic stress, aging, and neurodegenerative disease. Recently, we also found these cells to be abundant during normal development. These 'dark microglia' are tightly associated with blood vessels. They also interact extensively with synapses, suggesting their possible implication in the remodeling of neuronal circuits. To study this phenotype in the context of normal development and determine their origin from the bone marrow or embryonic yolk sac, this study was conducted using Flt3creRFPlox mouse model in which BMDC are selectively labelled, without radiation or chemotherapy that can affect the BBB permeability. The animals were sacrificed under steady-state conditions at different postnatal ages from birth until adulthood. Serial sections providing a non-biased representation of the brain were then immunostained for the microglia/macrophage marker IBA1 and imaged with a slide scanner to analyze the regional distribution, density, and morphology of the FLT3/IBA1-positive cells across development. 3D electron microscopy with immunostaining (array tomography technology) experiments are now underway to determine the origin of dark microglia.

2-A-6 Effects of perinatal exposure to nicotine on neuronal and glial cell number in the cingulate cortex and paraventricular nucleus of male rat offspring

Lydia Jeong[1], Dana Tabet[1], Xavier Seyer[1], Alison Holloway[2], Anne Konkle[1]

[1]University of Ottawa, [2]McMaster University

Nicotine exposure during pregnancy is widely established to have adverse consequences on the neurodevelopment of the offspring. Nevertheless, cigarette smoking during pregnancy still occurs due to nicotine dependency and consequences of withdrawal symptoms. Nicotine replacement therapy (NRT) has thus been used as a pharmacotherapy to aid in smoking cessation. However, there is insufficient data to determine whether NRT is safe for neurodevelopment. The objective of this study was to examine the effect of low levels of nicotine (concentration similar to those in the blood of pregnant mothers taking NRT) on the structure of cingulate cortex (Cg1 and Cg2) and paraventricular nucleus of the hypothalamus (PVN); we have previously shown effects in the entorhinal cortex. Female Wistar rats were treated daily with either 1.0 mg/kg of nicotine bitartrate or saline (s.c.) during pregnancy and until weaning. Brains of male offspring were collected at 26 weeks of age. Immunohistochemistry was performed on prepared brain sections to look at the number of NeuN and GFAP cells in these brain areas important in the stress response as well as learning. The results of a t-test for independent samples showed no significant effect of nicotine exposure on NeuN cell counts in Cg1 and Cg2, cautiously suggesting that NRT may be a safe alternative to smoking during pregnancy. GFAP cell counts and analysis of the PVN is in progress. Significant changes of cell numbers in these brain regions could translate to impairments in stress response and cognition in the offspring.

2-A-7 Axon elaboration in the developing retinotectal system is promoted by stimulation of neighbouring inputs

Tasnia Rahman[1], Martin Munz[2], Edward Ruthazer[3]

[1]McGill University, Montreal Neurological Institute, [2]Friedrich Meischer Institute, [3]McGill University - MNI

The specific aspects of patterned activity which underlie distinct changes in the developmental processes of axon branching, synapse formation and elimination remain poorly understood. Here, we combine in vivo multiphoton imaging techniques and visual stimulation protocols to elucidate how specific patterns of neuronal activity in the developing retinotectal circuit of albino Xenopus laevis tadpoles can alter the development of retinal ganglion cell (RGC) axon arbors. Although the majority of RGC axons innervate the contralateral side of the optic tectum, we take advantage of the fact that in a fraction of tadpoles, a stray axon will instead innervate the ipsilateral hemisphere. We can manipulate the activity of such an axon independently from its neighbours with a high degree of temporal control by presenting flashes of light to either

eye. We observed that contralateral eye stimulation led to larger arbors of ipsilaterally projecting RGC axons than did equivalent stimulation of the ipsilateral eye. Moreover, if vesicular release by the axon is blocked by expression of tetanus toxin, contralateral eye stimulation, but not ipsilateral eye stimulation, leads to an increased rate of branch addition. Altogether, our results suggest that visual stimulation of retinal inputs, presumably acting in concert to drive postsynaptic firing of tectal neurons, promotes exploratory branch elaboration of an adjacent unstimulated axonal arbor. In addition, when an axon successfully drives its postsynaptic partners to fire concurrently, branch stabilization is promoted instead.

2-A-8 Brainphys neuronal medium: a medium that promotes the maturation and synaptic function of human pluripotent stem cell (HPSC)-derived neurons in long-term cultures

Carmen Mak[1], Kasandra McCormack[1], Sam Lloyd-Burton[1], Allen Eaves[1], Terry Thomas[1], Sharon Louis[1], Vivian Lee[1]

[1]Stemcell Technologies

BrainPhys Neuronal Medium was developed based on a published formulation (Bardy et al., PNAS 2015) to support maturation and synaptic function of neurons in long-term cultures. Here, we describe the effect of BrainPhys on the electrophysiology of hPSC-derived neurons. Neural progenitor cells derived from hPSCs (XCL-1) were differentiated in BrainPhys with NeuroCult SM1 Neuronal Supplement and other growth factors (BP/SM1). Cells were cultured on microelectrode array (MEA) plates and activity was measured twice per week. Our data show that XCL-1-derived neurons cultured with BP/SM1 gradually became electrically active over an 18-week period. The mean firing rate (MFR) of neurons (n = 1; 128 electrodes) progressively increased from 0.1 Hz on day 30 to 1.6 Hz by day 125. The percentage of active electrodes (> 0.005 Hz) also increased from 30% on day 30 to 59% by day 125. Network bursts, a measure of synaptic connectivity, increased from 2 during a 10 minute interval on day 30 to 97 on day 125 , indicating synchronous firing was enhanced as neurons matured in BP/SM1. To confirm our data, we performed the same experiment on a different cell line (H9; n = 1), and we found that BP/SM1 consistently supports the electrical activity of neurons. Similar to the XCL-1 culture, there was an increase in MFR and network bursts when the H9-neurons were cultured in BP/SM1 over a 10-week maturation period. In summary, these results demonstrate that BrainPhys supports the physiological maturation and synaptic function of hPSC-derived neurons in long-term culture.

2-A-9 Nervous system development requires pro-survival protein Mcl-1.

Robert Flemmer[1], Joseph Opferman[2], Jacqueline Vanderluit[1]

[1]Memorial University of Newfoundland, [2]St. Jude Children's Research Hospital

Introduction: The nervous system arises from neural precursor cells (NPCs), a diverse, proliferating cell population consisting of neural stem cells and progenitor cells. Apoptosis, an active form of programmed cell death, plays key roles in regulating the total number of neurons and NPCs in the developing nervous system. Apoptosis is regulated by a balance between pro-survival and pro-death members of the Bcl-2 family of proteins. We have previously shown that pro-survival member Mcl-1 functions to promote not only NPC survival but also NPC differentiation. How Mcl-1 performs these functions has yet to be elucidated. Methods: To identify the mechanism by which Mcl-1 promotes NPC differentiation, I am identifying the NPC populations throughout the CNS that are dependent on Mcl-1 using a nervous system-specific Mcl-1 conditional knockout mouse (Mcl-1 CKO). Results: Apoptosis in the Mcl-1 CKO begins at E10 and follows the wave of neuronal differentiation and indicating that as NPCs begin to differentiate they become dependent on Mcl-1. Co-deletion of Mcl-1 and pro-apoptotic Bax rescues most of the NPC populations from apoptosis induced through Mcl-1 deletion alone but not all. I am further investigating the stage of neuronal differentiation when NPC populations become dependent on Mcl-1 using cell and stage-specific markers. Conclusion: Understanding how Mcl-1 functions in developmental neurogenesis will also shed light on how the nervous system develops from the primitive neural stem cell to the complex adult brain. Acknowledgements: This work was supported by an NSERC ope

2-A-10 Early subset of cerebellar nuclei neurons derived from mesencephalon in mice

Maryam Rahimi Balaei[1], Xiaodan Jiao[2], Behzad Yeganeh[3], Hassan Marzban[2]

[1]University of Manitoba, [2]University of Manitoba, School of Medicine, [3]University of Toronto

During cerebellar development, cerebellar nuclei (CN) neurons and Purkinje cells are the earliest born neurons. The CN represents the main output of the cerebellum, which is generated from the rhombic lip and the ventricular zone. We used whole mount/section immunohistochemistry, mouse cerebellar and embryonic cultures, western blotting, dye tracers and in situ hybridization

to examine the origin of a new subset of CN neurons from the mesencephalon during early cerebellar development. The isthmus, is a signaling center that distinguishes the mesencephalon from the rhombencephalon. Our results show that a subset of CN neurons, which are immunopositive for α-synuclein (SNCA) and orthodenticle homeobox 2 (Otx2), originate from the mesencephalon and cross the isthmus toward the rostral end of the nuclear transitory zone. Double immunostaining of the SNCA with Otx2 or p75 neurotrophin receptor (p75ntr) indicates that these cells are derived from neural crest cells. We also showed that this population of neurons with nerve fibers terminates at the subpial surface of putative lobules VI/VII. The SNCA+/Otx2+/p75+ cells, which divide the cerebellar primordium into rosterodorsal and caudoventral compartments, show increased cleaved caspase-3 activation. These results strongly suggest that early CN neurons originate from the mesencephalic neural crest population and cross the isthmus and contribute in CN. Their temporary presence in the nuclear transitory zone suggests these neurons/fibers play a regulatory role as a signaling center, such as axonal guidance and neuronal migration

2-A-11 Cell-dependent aging of cortical microcircuit correlates with mood and cognitive behaviors

Rammohan Shukla[1], Thomas Prevot[2], Leon French[2], Ruth Isserlin[1], Brad Rocco[2], Mounira Banasr[2], Gary Bader[1], Etienne Sibille[2]

[1]University of Toronto, [2]CAMH

Aging is accompanied by altered thinking, feeling and locomotion functions that depend to some extent on information processing by brain cortical cell microcircuits. We hypothesized that age-associated long-term functional and biological changes are mediated by gene transcriptomic changes within and across the neuronal cell types forming these microcircuits, namely excitatory pyramidal cells (PYC) and inhibitory GABA neurons expressing Vip, Sst, and Pvalb. To address this hypothesis, we assessed age-associated changes in young and old male mice using a battery of tests for anxiety and cognitive behaviors and then performed frontal cortex cell-type specific molecular profiling, using laser-capture microscopy and RNA-seq. Behavioral and molecular results were analyzed for coordinated changes using ontological and integrative network biology approaches. A principal component analysis revealed three independent behavioral dimensions related to age and cognition, locomotion and working memory. The four cell types displayed distinct changes in age-related transcriptomes, pathway profiles, and structure of gene co-expression network, with gene coexpression modules

correlating with behavioral dimensions in cell type-specific ways. A cell-specific change in metabolic and cell signaling pathways and markers of neuronal vulnerability and neuronal resilience reveals high and low vulnerabilities of PYCs and PV neurons respectively. Collectively, the data suggest an order of neuronal vulnerability and direction of cellular activity with respect to age and behavior dimensions.

2-A-12 Myelination of the developing Xenopus laevis retinotectal system

Zahraa Chorghay[1], Anne Schohl[1], Nicholas Marsh-Armstrong[2], Ragnhildur Thóra Káradóttir[3], Edward Ruthazer[1]

[1]McGill University - MNI, [2]UC Davis, [3]U of Cambridge - Wellcome Trust MRC Stem Cell Institute

Precise timing of neuronal communication is important for proper circuit formation and function during development and throughout the lifetime of an organism. Myelin, the insulatory material around axons, modulates axonal conduction velocities of the action potentials that mediate neuronal communication. Despite its importance in functional circuits, relatively little is known about how neuronal activity impacts myelination in the developing brain. Crucial support for the concept of myelin plasticity comes from the observation that changes in neuronal activity, in the form of experience or of experimental manipulation, alter characteristics of the myelin and of myelinating glial cells, including oligodendrocytes (OLs) and their precursors. Our study aims to use the Xenopus laevis retinotectal system to investigate how changes in sensory experience, through visual stimulation and deprivation, can alter myelination in vivo. First, we are characterizing the timecourse of myelination during Xenopus development by immunohistochemistry. Second, we are applying the Xenopus tadpole model for in vivo visualization of myelination by multiphoton imaging of retinal axons, using CASPR-GFP to label their nodes of Ranvier and MBP-GFP transgenic animals to visualize myelin ensheathment by OLs. To date, we have observed that in the visual system of tadpoles, the onset of myelination occurs at stage 48, starting around the optic chiasm and extending peripherally at later stages. Our work will provide novel insights into the process of activity-dependent myelination in the developing brain.

2-B-13 Metabolic triggers of slow wave brain states

Axita Shienh[1], Claire Scavuzzo[1], Clayton Dickson[1]

[1]University of Alberta

Brain lactate increases during waking and rapid eye movement (REM) sleep and decreases during non-REM sleep. We hypothesized that increased extracellular brain L-lactate, a byproduct of astrocyte metabolism, and an oxidative fuel for neurons, might also function to promote the state of non-REM sleep. Using the urethane anesthesia model of sleep, in which alternations between REM- and non-REM-like states occur spontaneously, we evaluated changes in brain state and extracellular L-lactate as a function of the following manipulations: 1) i.v. L- lactate, 2) i.v. D- lactate; 3) i.v. vehicle control; or 4) inhaled 100% oxygen. Similar to natural sleep, brain L-lactate levels increased and decreased, respectively, concomitant with alternations in REM-, and non-REM-like states. Injections of both L- and D- lactate promoted the non-REM state, but the influence of L-lactate was longer-lasting. L-lactate, but not D-lactate, also increased extracellular L-lactate levels. Interestingly, hyperoxia also increased brain L-lactate and similarly enhanced the non-REM state, while control injections produced no changes in either measure. Our data suggests that increases in brain lactate promote non-REM states. Given that D-lactate can act on the same Gi/o-coupled metabotropic receptors as L-lactate, but cannot be oxidized to produce energy, this suggests that brain lactate levels may act to promote non-REM states via both direct signaling and indirect metabolic mechanisms.

2-B-14 Selective melatonin MT2 receptor ligands relieve neuropathic pain through modulation of brainstem descending antinociceptive pathways and opioid interactions

Luca Posa[1], Martha Lopez-Canul[1], Stefano Comai[2], Serena Boccella[3], Sabatino Maione[3], Vinicio Granados-Soto[4], Gabriella Gobbi[1]

[1]McGill University, [2]Vita-Salute University, [3]Università di Napoli, [4]Centro de Investigación y de Estudios Avanzados del I.P.N

Aim: Neuropathic pain is a health problem for which few treatments are available. Preclinical studies show that melatonin (MLT) and its related selective agonists of MT2 receptor have analgesic properties, likely through opioid (OR) receptors. We determined the effects of the selective MT2 receptor partial agonist (UCM924) in two rat neuropathic pain models and examined its supraspinal mechanism of action. Methods: L5-L6 spinal nerve ligation and spared nerve injury models were used to evaluate neuropathic allodynia and in-vivo electrophysiological recording of ON and OFF cells in the periaqueductal grey-rostral ventral medulla (PAG-RVM) projection were collected to determine the mechanism of action. Results: In both models, UCM924 produced a prolonged antinociceptive effect that is: dose-dependent,

superior to a high dose of MLT and comparable with gabapentin, but without motor coordination impairments. Using in-vivo electrophysiology combined with tail-flick, we observed that microinjection of UCM924 into the PAG decreased tail-flick response, depressed the firing activity of ON cells, and activated the firing of OFF cells. Importantly, non-selective (naloxone) and selective opioid mOR antagonist (CTOP), but not selective dOR antagonist (naltrindole) blocked the antinociceptive effects of UCM924 in the neuropathic model and its effect on ON and OFF cells. Conclusions: Altogether, UCM924 have analgesic properties by modulation of descending antinociceptive pathways and this effect is mediated by mOR. MT2 receptors may represent a target in the treatment of neuropathic pain

2-B-16 Molecular mechanisms underlying Pannexin 1 trafficking in neural cells

Anna Epp[1], Leigh Wicki-Stordeur[2], Andrew Boyce[3], Leigh Anne Swayne[1]

[1]University of Victoria, [2]University of British Columbia, [3]University of Calgary

Pannexin1 (Panx1) channels are enriched in the central nervous system (CNS) where they regulate neuronal activity and development, in part through mediating release of ATP. The molecular mechanisms regulating Panx1 localization are not fully understood. Previous studies from other and us have identified the C-terminus (CT) as a key regulator of Panx1 localization. For example, the Panx1 CT interacts with actin and Arp3, which is thought to play a role in stabilizing Panx1 at the cell surface. Strikingly, deletion of the entire CT was previously reported in HEK293T cells to disrupt normal subcellular distribution, but addition of the Panx1CT was not sufficient to localize the intracellular Panx2 to the plasma membrane in N2a cells. Together these earlier findings suggest that the Panx1CT is necessary but not sufficient for Panx1 localization to the plasma membrane; however, the precise amino acid region(s) within the CT that is responsible for cell surface localization has not yet been identified, nor have potential differences in different expression systems. Here we compare the surface expression of several new Panx1 deletion mutants using cell surface biotinylation and confocal microscopy. In parallel we also confirm the ability of these deletion mutants to form hexamers using crosslinking assays. This work will contribute to our overall goal of understanding of the mechanisms regulating Panx1 localization, which have important implications for its function in the central nervous system.

2-B-17 Novel role of cGMP signaling in hippocampal synaptic plasticity and mouse cognitive function

Jelena Borovac[1], Thomas Luyben[1], Keizo Takao[2], Kenichi Okamoto[3]

[1]University of Toronto, [2]University of Toyama, [3]Lunenfeld-Tanenbaum Research Institute

Activity-dependent structural and functional modulation of the synapse is essential for learning and memory. cGMP signaling is thought to modulate synaptic plasticity, but its function in hippocampal synaptic structure and the mechanism by which it regulates synaptic function remains elusive. Here, we demonstrate the function of cGMP in structural plasticity of dendritic spines in rodent hippocampal CA1 pyramidal neurons and reveal a novel role of cGMP in functional plasticity of hippocampal DG granule neurons and learning/memory. Strong synaptic activation induces synapse enlargement called structural long-term potentiation (sLTP), reorganizing synaptic function through structural change. We found that postsynaptic cGMP signalling is involved in depotentiation of cAMP-dependent sLTP by blocking the cGMP/PKG pathway. Furthermore, using a two-photon optogenetic approach to activate light-sensitive guanylyl cyclases at target dendritic spines, we revealed that an increase in the level of postsynaptic cGMP was sufficient to block the cAMP effect on structural potentiation, but not induction of sLTP, suggesting a crucial inhibitory role of cGMP in cAMP-sLTP. To address the role of cGMP on the neural circuit level, we next studied the effect of cGMP signal at the medial perforant path synapses of the dentate gyrus (PP-DG) on functional LTP and mouse behavior. By optogenetic manipulation of cGMP in the mouse hippocampal DG granule neurons, we revealed an effect of cGMP on hippocampal LTP and learning/memory.

2-B-18 Metabolically slowing down the brain during sleep

Claire Scavuzzo[1], Axita Shienh[1], Clayton Dickson[1]

[1]University of Alberta

Providing fuel to the brain in terms of increased blood levels of oxygen or L-lactate increases extracellular brain L-lactate and promotes slow-waves states (SWS) during urethane anesthesia. To test if directly increasing extracellular brain lactate might promote a similar SWS bias, we made local field potential and extracellular lactate recordings in urethane anesthetized rats demonstrating spontaneous sleep-like cyclic alternations and tested the influence of intracranial infusions of 1) L- lactate, 2) D- lactate; or 3) vehicle control. L-lactate infusions at single circumscribed sites in either neocortex or hippocampus increased brain L-lactate globally

throughout the brain, as compared to baseline conditions. They also biased the entire forebrain towards SWS. Neither D-lactate nor vehicle infusions altered extracellular L-lactate or brain state as compared to pre-infusion measures. Thus, single point infusions of L-lactate, but not D-lactate, can increase brain-wide L-lactate levels and promote global forebrain SWS. Given that only L-lactate can be used as a fuel but both D- and L-lactate can act as ligands for Gi/o-coupled lactate receptors, our data suggest that indirect metabolic mechanisms support the global nature of brain lactate and forebrain state changes; which in turn promote SWS. It is likely that a syncytium of astrocytes is responsible for the propagation of this brain-wide effect.

2-B-19 The cellular and molecular mechanisms underlying the role of LIMK1 in synaptic plasticity

Youssif Ben Zablah[1]

[1]*University of Toronto/ Hospital for sick children*

My research has focused on identifying the role of LIMK1 in synaptic plasticity. Based on previous studies which have shown that LIMK1 plays role in synapses and dendritic spines structure and with an aim to further investigate the role of LIMK1 in neuronal circuits in vivo, my lab has generated LIMK1 knockout mice and has presented genetic and physiological evidences supporting the hypothesis that LIMK1 is critically involved in spine morphogenesis and synaptic function via regulation of actin cytoskeleton. LIMK1 knockout mice have abnormalities in dendritic spines, synaptic function and learning and memory. Recently, it has been found that LIMK1 interacts and phosphorylates CREB in hippocampal neuroprogenitor cells. Moreover, LIMK1 phosphorylates CREB at serine-133, which is the site that is widely believed to activate CREB function. In addition, it has been shown that LIMK1 regulates long-term memory and synaptic plasticity via the transcriptional factor CREB. In my work, I have focused on providing evidences that changes in neuronal activity and synaptic plasticity associates with activation of LIMK1. Furthermore, I found that nuclear translocation of LIMK1 occurs during synaptic plasticity and learning and memory. However, I have yet to delineate the molecular mechanisms, which underlie the nuclear translocation of LIMK1. Furthermore, the role and significance of LIMK1 nuclear translocation remain unanswered question. Therefore, my future work will focus on characterizing the molecular mechanisms of nuclear translocation LIMK1 during synaptic plasticity.

2-B-20 Differential expression pattern of the endocannabinoid system in the monkey primary visual cortex

Ryan Kucera[1], Joseph Bouskila[2], Michel Toutoungy[1], Karys Peterson[1], Roberta Palmour[2], Jean-François Bouchard[1], Maurice Ptito[1]

[1]Université de Montréal, [2]McGill University

The expression and localization of the endocannabinoid system have been well characterized in the monkey retina and dorsal lateral geniculate nucleus (dLGN). However, few data are available on primate cortical visual structures. The goal of this study is to characterize the expression and localization of the cannabinoid receptor type 1 (CB1R), the synthesizing enzyme N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD), and the degradation enzyme fatty acid amide hydrolase (FAAH) in the monkey primary visual cortex (V1). Using Western blots and immunohistochemistry, we investigated the laminar expression patterns of CB1R, NAPE-PLD, and FAAH across the rostrocaudal axis of the vervet monkey (Chlorocebus sabaeus) area V1. CB1R, NAPE-PLD, and FAAH were expressed in V1 throughout the rostrocaudal axis. CB1R showed very low staining in layer (L) 4, with higher expression in all other layers, especially L1, followed by L2 and L3. NAPE-PLD and FAAH expression patterns were similar, but not quite as low in L4. The low level of CB1R in L4 indicates less direct endocannabinoid modulation of V1 afferents from the dLGN, but that modulation may occur via the higher expression of CB1R in L2 and L3 on the way to the dorsal and ventral visual streams. This is further supported by the higher expression of NAPE-PLD and FAAH in these layers. These data indicate that CB1R can influence the network of activity patterns in the visual streams after the visual information has reached V1, and thus may influence visual perception.

2-B-21 Dynamic behavioral and molecular changes induced by chronic stress exposure in mice: importance of astroglia integrity

Thomas Prevot[1], Keith Misquitta[1], Corey Fee[1], Dwight Newton[1], Hyunjung Oh[1], Etienne Sibille[1], Mounira Banasr[1]

[1]CAMH

Major depressive disorder (MDD) is associated with molecular changes within GABA cells, astrocytes and synapses in the prefrontal cortex (PFC) and similar changes are reported in stress-based rodent models of depression. To identify the sequence of events affecting each cell compartment we characterized the time-dependent cell-specific changes during chronic stress

exposure and their impact on behavioral outcomes to identify potential key features in the onset of pathological states. Using C57 mice (50% ♀) we determined the effects of chronic restraint stress (CRS - 1h, 2x day) on anxiety- and anhedonia-like behavior, and on GABA, astrocytic and synaptic marker expression (qPCR and western blot analysis) in the PFC after 7 to 35 days of CRS. CRS induced anxiety-like behavior in mice regardless of the duration of CRS but also a progressive increase in anhedonia-like behavior after 21d of exposure. At the cellular level, GABA marker expressions were decreased first, followed by astrocytic markers and synaptic markers. Interestingly, while anxiety-like behaviors correlated with GABA marker expression, astrocytic marker correlated with both anhedonia- and anxiety-like deficits, suggesting a critical role of astrocyte in the maladaptive response to stress. We confirm that chronic stress induces time-dependent cell-specific alterations that are linked to various behavioral outcomes. Altogether, our results suggest that astroglial dysfunction would be a critical momentum in the response to stress leading to the pathological state associated with stress-related illnesses such as MD

2-B-22 An acute session of continuous theta burst stimulation (cTBS) decreases dopamine release in non-human primate striatum

Lucero Aceves Serrano[1], Jason Neva[1], Katelyn Brown[1], Lara Boyd[1], Doris Doudet[1]

[1]University of British Columbia

Theta Burst Stimulation (TBS), a patterned high-frequency form of repetitive transcranial magnetic stimulation (rTMS), can produce long-lasting changes in cortical excitability. A session of excitatory rTMS has been shown to decrease raclopride binding by PET, presumably through an increased striatal dopamine release. Here, we tested the effect of a single session of continuous TBS (cTBS), which can decrease cortical excitability) on dopamine release by assessing the changes of raclopride, a D2 antagonist, before and immediately after the administration of cTBS in non-human primates (NHP). Two 11C-Raclopride scans were acquired, one at baseline and immediately after cTBS. NHP received either cTBS or sham stimulation over left primary motor cortex (M1). For cTBS, a continuous train of 600 pulses was applied for 40 seconds at 90% of resting motor threshold. Sham stimulation was delivered with the same parameters but with the magnetic field facing away from the head of the subject. NHP that received the cTBS showed an increase in raclopride binding in caudate and putamen. Surprisingly, the increase in raclopride binding was observed in both left and right striatum. We showed that cTBS-induced modulation of M1 may indirectly affect dopamine release at the

ipsilateral and contralateral striatum in NHP. Increased raclopride binding suggests that there is a reduction in dopamine release in the striatum. This may be mediated through inhibition of local circuitry within M1, which modulates activity through cortico-striatal projections and interhemispheric connections.

2-B-23 An interaction between monoglycosylated form of PrPc and GluA2 regulates Ca2+ impermeable AMPA receptor trafficking to the neuronal lipid rafts

Hajar Miranzadeh-Mahabadi[1], Sathiya Sekar[1], Graham Collingridge[2], Changiz Taghibiglou[1]

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

GluA2-containing AMPARs are distributed in both lipid rafts and non-rafts compartments of neuronal plasma membrane. We discovered that GluA2-containing AMPA receptor (AMPAR) requires an interaction with mono-glycosylated form of cellular prion protein (PrPc) for trafficking to the neuronal lipid rafts. The N-terminal polybasic region of PrPc interacts with N-terminal domain of GluA2. Our data indicate that this interaction occurs co-translationally and is necessary for GluA2-containing AMPAR trafficking to the lipid rafts and its localization/anchoring there. Any disruption of this interaction triggers GluA2 subunit endocytosis. Confocal imaging and electron microscopy confirmed the co-localization of PrPc/GluA2 and the importance of polybasic region in this interaction. These observations were also confirmed in lipid rafts and non-raft isolated fractions from PrPc-KO mouse cortices when compared with the wild type mouse cortices. We also noticed a significant behavioral change in wild type mice after intraperitoneal injection of the TAT-fused interfering/disrupting peptide. Together, these results showed a previously unknown functional interaction between mono-glycosylated form of PrPc and GluA2 subunit of AMPA receptor with physiological and behavioral consequences.

2-B-24 Role of JAK2-STAT3 in Synaptic and Homeostatic Plasticity

Sun-Lim Choi[1], Eric Salter[2], Tomas Sanderson[3], Graham Collingridge[2]

[1]Mount Sinai Hospital, [2]University of Toronto, [3]University of Bristol

There are many published studies on synaptic plasticity and homeostatic synaptic plasticity. However, the extent to which molecules or signaling pathways are shared between these distinct

plasticity mechanisms remains unclear. We found that JAK2 and STAT3, which are necessary for input-specific long-term depression (LTD)1, are differentially expressed 48 hr after bicuculline (Bic) treatment, but not after tetrodotoxin (TTX) treatment, of cultured hippocampal neurons. This effect, which is associated with synaptic down-scaling, occurred in a NMDA receptor-dependent manner. The mRNA levels of all known JAKs and STAT isoforms were not altered after Bic treatment. Since STAT3 mRNA has two conserved cytoplasmic polyadenylation elements (CPE), we examined the poly A tail which was elongated after Bic treatment. These data suggest that the JAK2-STAT3 pathway may have an important role homeostatic plasticity as well as input-specific synaptic plasticity.

2-B-25 Enhancement of DA efflux by Heantos-4, a traditional herbal treatment for opiate addiction, involves activity-dependent release modulated by antagonism at the presynaptic D2 autoreceptor

Soyon Ahn[1], Kitty So[1], Giada Vacca[1], Haiyan Zou[1], Maya Nesbit[1], Peter Axerio-Cilies[1], Tran Van Sung[2], Anthony Phillips[1]

[1]University of British Columbia, [2]Vietnam Academy of Science and Technology

Heantos-4 is a modern formulation of extracts from twelve medicinal plants and is currently in use as an in-clinic treatment for opiate detoxification in Vietnam. It has no addictive properties and is effective in mitigating withdrawal symptoms. Given the potential value of this treatment in the face of the current epidemic opioid crisis, we conducted a series of experiments to elucidate possible mechanisms by which Heantos-4 may influence a key neural correlate of addiction, brain dopamine (DA) function. Using microdialysis in combination with HPLC-ED, we show that DA efflux in the nucleus accumbens (NAc) is increased in a dose-dependent manner following oral administration of Heantos-4. These Heantos-4 evoked DA increases are dependent on synthesis of new DA, uptake into vesicles by the vesicular monoamine transporter 2, Ca2+-mediated exocytosis of vesicles, and K+-sensitive changes in membrane potential. All are mechanisms of DA release that are under close regulation by the D2 autoreceptor in the presynaptic terminal. Accordingly, we also demonstrate that Heantos-4, in common with the D2 antagonist eticlopride, reverses the inhibition of DA efflux induced by autoreceptor-specific doses of the D2 agonist quinpirole. Finally, using mass spectrometry and high pressure liquid chromatography, we provide evidence that l-stepholidine, a phytochemical previously identified in Heantos-4, crosses the blood-brain barrier following oral administration and accumulate in

sufficient quantities to influence D2 autoreceptor, thereby modulating the activity of the mesolimbic DA system.

2-B-26 Extracellular cardiolipin modulates microglial phagocytosis and their cytokine secretion in a toll-like receptor (TLR) 4-dependent manner

Tyler Wenzel[1], Caitlin Pointer[1], Andis Klegeris[2]

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

Cardiolipin (CL), a phospholipid normally embedded in mitochondrial membranes, can serve as a signaling molecule when released extracellularly. This has been demonstrated in peripheral tissues were CL is released in response to cell injury and death. It is unknown whether CL plays a similar role in the central nervous system. Microglia, the brain macrophages, respond to cell death, but it is not known how they recognize dying cells. We hypothesized that extracellular CL is one of the signaling molecules released by degenerating and dying brain cells, which induces or modulates microglial immune response. We studied the effects of extracellularly applied CL on primary murine microglia, BV-2 murine microglia, and human THP-1 monocytic cells as a microglial model. CL (5-20μM) added to cell culture medium induced the secretion of tumor necrosis factor (TNF)-alpha and monocytic chemoattractant protein (MCP)-1, and increased the phagocytic activity of BV-2 cells. CL (5-20μM) induced the release of TNF-alpha and MCP-1, as well as increased the phagocytic activity of THP-1 cells. CL-induced upregulation of the phagocytic activity of primary murine microglia was blocked by anti-toll-like receptor (TLR) 4 antibodies. When CL (5-20μM) was added to lipopolysaccharide (LPS)-stimulated BV-2 or THP-1 cells, it decreased the secretion of TNF-alpha, and MCP-1 without reducing viability of cells. We demonstrate for the first time that extracellular CL can regulate neuroimmune processes by modulating select microglial functions in a TLR4-dependent manner.

2-B-27 The X-linked intellectual disability gene, zDHHC9, is essential for dendritic maintenance and inhibitory synapse formation

Jordan Shimell[1], Bhavin Shah[1], Stuart Cain[1], D. Blair Jovellar[1], G. Stefano Brigidi[1], Igor Tatarnikov[1], Naila Kuhlmann[1], Dayne Beccano-Kelly[1], Austen Milnerwood[2], Terrance P Snutch[1], Shernaz Bamji[1]

[1]University of British Columbia, [2]Montreal Neurological Institute

Palmitoylation is the most common lipid modification in the brain and plays an essential role in protein trafficking and signalling. Palmitoylation is mediated by a family of 23 zDHHC enzymes and 9 have been associated with diseases of the brain. Loss-of-function mutations in zDHHC9 have been identified in as many as 2% of all patients with X-linked intellectual disability (XLID). Of these, >75% have been diagnosed with epilepsy, underscoring the importance of zDHHC9 in the development of the brain. Here we demonstrate that zDHHC9 plays an important role in maintaining the length and complexity of dendritic arbors as well as the formation and maintenance of inhibitory synapses. Indeed, loss of zDHHC9 function in cultured hippocampal neurons leads to shorter dendritic arbors and fewer inhibitory synapses, enhancing the ratio of excitatory to inhibitory inputs onto mutant cells. We also show that zDHHC9 knockout mice exhibit increased seizure activity and altered electrophysiological parameters, consistent with our in vitro data. This work provides a plausible mechanistic explanation for how loss of zDHHC9 function may lead to XLID with epilepsy.

2-B-28 Amyloid β reduces pannexin-1 channel opening during ischemia through an mGluR1-mediated mechanism

Laura Palmer[1], Andrew Boyce[1], Alexander Lohman[1], Connor Anderson[1], Roger Thompson[1]

[1]University of Calgary

Alzheimer's disease (AD) is associated with over-production of the amyloid β (Aβ) protein. Stroke has been identified as an important risk factor of AD, and accounts for up to five-fold increase in risk of developing AD. Interestingly, hypoxia upregulates Aβ production. We hypothesized that Aβ may play a physiological role during hypoxia, such as modulating the anoxic depolarization (aDP). The aDP is a large inward current that occurs in response to hypoxic glutamate release, activating N-methyl-D-aspartate receptors (NMDARs). Previously, our group has demonstrated activation of pannexin-1 (Panx1) channels downstream of NMDARs during hypoxia. Furthermore, mGluRs are known to regulate NMDARs, and also play a role in anoxia. Since NMDARs/mGluRs are a known target of Aβ, we hypothesized that Aβ could protect against ischemic pannexin-1 channel opening. Using whole-cell patch clamp electrophysiology in rat hippocampal slices, the aDP was assayed using low oxygen (~5 mmHg) artificial cerebral spinal fluid. We found that low concentrations (pM to nM) of exogenous Aβ attenuated the anoxic depolarization, and also blocked Panx1 opening on an NMDA overstimulation assay. Reducing endogenous Aβ levels using L-685,458 increased aDP severity. Human Aβ also had a protective effect on the aDP, and mice slices overexpressing Aβ oligomers were protected

compared to those of wild-type littermates. Lastly, the protective Aβ effect on the aDP was reversed with co-application of mGluR1 antagonists. These data suggest a novel modulation of Panx1 opening by mGluR1, which is regulated by Aβ.

2-B-29 Prefrontal responses to optogenetic release of endogenous acetylcholine depend on expression of alpha5 nicotinic receptors

Sridevi Venkatesan[1], Daniel Sparks[1], Evelyn Lambe[1]

[1]University of Toronto

Layer 6 pyramidal neurons of the prefrontal cortex are excited robustly by acetylcholine (ACh) and are a major source of projections to the thalamus. Hence, they are postulated to be involved in top-down cholinergic modulation of attention. The α5 nicotinic receptor subunit encoded by Chrna5 is an accessory subunit that is heavily expressed in layer 6 of the PFC and may affect receptor conductance and desensitization properties. Previous studies have shown that α5-/- mice are impaired during demanding attentional tasks. However, the role of Chrna5 in the cellular and network response to endogenous ACh is unknown. Here, we investigate the role of the α5 nicotinic subunit in the response to optogenetic cholinergic stimulation, using whole cell recordings in brain slices from littermate wildtype and α5-/- mice expressing channelrhodopsin2 in cholinergic neurons. Our results show that the response to light-evoked ACh release is significantly attenuated in α5-/- mice. Wild-type mice show a state of cholinergic-evoked persistent activity, which greatly exceeds the duration of light stimulation. Such activity is rare in α5-/- mice and has slower kinetics when it does occur. In voltage clamp, the inward current elicited by ACh release is reduced in the α5-/- mice. In ongoing work, we are probing the contributions of specific cholinergic receptors in relation to Chrna5 genotype. Taken together, these experiments will demonstrate the specific role of the α5 subunit in the cholinergic control of attention circuitry.

2-B-30 What happens when astrocytes talk to neurons? A PI3K interactome in neurons following exposure to astrocyte secretome

Samih Alqawlaq[1], Izhar Livne-Bar[2], Darren Chan[1], Jeremy Sivak[1]

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

Astrocyte-neuron interactions are essential to normal vision in the eye. These interactions maintain the survival and function of neurons, as well as protect them from various neurochemical insults. The current research aims to identify signaling mechanisms activated by astrocyte-secreted factors, particularly along the phosphatidylinositol-3-kinases (PI3K) pathway. Astrocyte conditioned media (ACM) was collected from our established primary culture model. ACM rescued glutamate-induced cell death in neuronal Ht22 cells, and in primary cortical neurons. A small molecule screen was carried out to identify induced pathways, namely the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K). Immunoblotting was then carried out to confirm the activation of PI3k in neurons by ACM. Cross-linked PI3K was immunoprecipitated in neurons treated with ACM and control media to identify its major interactors, followed by ITRAQ isobaric labeling and mass spectroscopy analysis. The pharmacological screen revealed a number of inhibitors targeting the PI3K pathway. The PI3K inhibitor ZSTK474, and AKT inhibitor GSK690693 each eliminated 90% of ACM-mediated activity in both Ht22 cells and primary neurons. ACM treatment was sufficient to induce AKT phosphorylation by 30 minutes. PI3K interactome analysis identified a number of upstream and downstream targets activated in neurons following ACM exposure. Our findings demonstrate that ACM neuroprotection in neurons is mediated through PI3K, and key interactors. This will enable additional exploration of protective astrocyte secreted factors.

2-B-31 Lactate from astrocytes: a critical energy source for the learning-induced translation required for long-term memory

Giannina Descalzi[1], Virginia Gao[1], Michael Steinman[1], Cristina Alberini[1]

[1]New York University

Memory formation requires de novo protein synthesis in neurons, a process that requires large amounts of energy. Several studies indicate astrocytic lactate is an efficient energy substrate for neurons. We have previously shown that inhibitory avoidance learning leads to astrocytic glycogenolysis and lactate transport from astrocytes to neurons in the rat hippocampus. Blocking this process prevents memory formation and blunts learning-dependent induction of proteins such Arc/Arg3.1. Both memory and molecular impairments produced by inhibiting astrocytic glycogenolysis and lactate transport are rescued by hippocampal injection of lactate. Here we asked: what is the role of lactate in neurons? We found that inhibition of astrocytic glycogenolysis or downregulation of glia monocarboxylate transporters (MCT) 1 and 4, disrupt memory formation, and this effect is rescued by pyruvate or the ketone body B3HB.

Furthermore, downregulation of the neuronal monocarboxylate transporter MCT2 prevented these rescuing effects. We found that learning-induced Arc expression in excitatory neurons is blocked if glycogenolysis is inhibited, and this blockade is rescued by either lactate or pyruvate. In addition, in vivo surface sensing of translation (SUnSET) revealed that blocking hippocampal glycogenolysis prevents the increase in de novo learning-induced translation in neurons, which was rescued by either lactate or pyruvate. We thus conclude that astrocytic lactate provides metabolic support critical for the learning-induced translation in neurons that is necessary for memory formation.

2-B-32 Transcriptomic correlates of electrophysiological diversity within and across cell types

Claire Bomkamp[1], Shreejoy Tripathy[1], Paul Pavlidis[1], Ann Marie Craig[1]

[1]University of British Columbia

Large-scale gene expression profiling allows unprecedented access to the full transcriptome of cell types or even single cells. Here, we combined publicly accessible cell type-specific and single-cell gene expression with neuron electrophysiology and morphology measurements. Building on our previous work correlating gene expression with electrophysiology, we found that methods that focus on variation within broad cell classes (i.e., partial correlation) yielded fewer significant correlations. However, those that were identified were much less likely to be driven by overall differences between excitatory versus inhibitory cell types and instead reflected graded phenotypic differences between cell types within these broad cell classes. Next, using data from Patch-Seq experiments, allowing simultaneous single-cell characterization of gene expression, electrophysiology, and morphology, we tested whether the correlations derived across cell types also held true within cell types. Lastly, to investigate the possibility of functional relationships between genes correlated with a given property, we incorporated data from gene regulatory experiments, including ChIP-Seq assays. We found some evidence for correlation of both transcription factors and their targets with the same electrophysiological property. In summary, we have identified a number of relationships between gene expression and electrophysiology which we hope will provide testable hypotheses for future studies.

2-B-33 Investigating the function of the complement cascade in hippocampus synaptic plasticity

Eric Salter[1], Sun-Lim Choi[2], John Georgiou[3], Graham Collingridge[1]

[1]University of Toronto, [2]Mount Sinai Hospital, [3]Lunenfeld-Tanenbaum Research Institude, Mount Sinai Hospital

Background: Aberrant activation of the complement cascade leads to synapse loss in Alzheimer's disease models, and is implicated in the pathogenesis of schizophrenia. Neuronal activity is able to regulate complement activation and synapse pruning by microglia, however the precise activity patterns leading to complement activation are completely unknown. Studies have demonstrated that the complement cascade activates molecular pathways which are also involved in NMDAR-dependent long-term depression (NMDAR-LTD), suggesting that the complement cascade can regulate this form of synaptic plasticity. Hypothesis: The complement cascade is involved in the induction of NMDAR-LTD in the hippocampus. Methods: Using acute brain slice electrophysiology, we measured NMDAR-LTD in area CA1 from P13-P17 mice with a genetic deletion of either Cd11b or C3. Results: There was no difference in the magnitude of NMDAR-LTD induced by low-frequency stimulation in either male or female Cd11b-/- mice compared to littermate controls; metabotropic glutamate receptor (mGluR)-LTD was similarly unaltered. However, in female C3-/- mice, there was a significant reduction in the magnitude of NMDAR-LTD. Discussion: This study provides novel insights into the function of the complement cascade in the hippocampus, which suggests that complement component C3 is critical for the induction of NMDAR-LTD independent of the complement cascade. The knowledge gained in this study will be crucial for determining the precise role of this pathway in brain disorders including Alzheimer's disease and schizophrenia.

2-B-34 Cholinergic regulation of deleted-in-colorectal cancer facilitates persistent firing in the entorhinal cortex.

Stephen Glasgow[1], Julien Gibon[2], Philippe Séguéla[1], Edward Ruthazer[3], Timothy Kennedy[1]

[1]Montreal Neurological Institute, [2]University of British Columbia - Okanagan, [3]McGill University - MNI

Changes in the structure and function of synapses underlie learning and memory. We have recently demonstrated a novel role for netrin-1, a chemotropic guidance cue, in activity-dependent synaptic plasticity. These findings suggest that dynamic trafficking of deleted-in-

colorectal cancer (DCC), a canonical receptor for netrin-1, may contribute to on-going modification of synapse function. We have previously demonstrated that the plasma membrane distribution of DCC is regulated by strong depolarization induced by changes in extracellular K+ concentration. Excitatory neuromodulation, such as cholinergic receptor activation, may contribute to network connectivity via promoting dynamic changes in DCC distribution through potent depolarization of membrane potential. We show that muscarinic and nicotinic cholinergic-induced membrane depolarization recruits DCC to the plasma membrane of cultured cortical neurons. Cholinergic receptor activation also increases DCC co-localization with both pre- and post-synaptic markers. Further, bath application of netrin-1 facilitates cholinergic-mediated persistent firing activity in layer V entorhinal neurons in acute adult brain slices, a form of intrinsic cellular activity that has been associated with working memory processes. Together, these findings show that acetylcholine can modulate cortical synapses through the active recruitment of DCC, and this can, in turn, promote synaptic plasticity via enhancement of netrin-1-signaling.

2-B-35 Frequency-dependent coupling between neuronal activity and mitochondrial Ca2+ dynamics in situ

Chris Groten[1], Alexa Nelson[2], Brian MacVicar[2]

[1]Post-doc, [2]University of British Columbia

Alterations in mitochondrial energy production in neurons have dramatic consequences for brain health. Despite this, the mechanisms by which mitochondria influence/respond to neuronal function have not been fully examined in native brain tissue. As a first step towards understanding potentially unique aspects of this relationship, we examined a role for mitochondrial Ca2+ dynamics in the CNS. While this property has long been associated with pathological changes in ATP/ROS production and apoptotic signalling, its significance for brain function is unclear. To address this, I utilized two-photon microscopy and examined the relationship between action potential frequency and cytosolic Ca2+/mitochondrial Ca2+ in neurons from cortical brain slices. Current-clamp recordings from pyramidal neurons expressing the mitochondrial Ca2+ reporter mitoRGECO1.0 revealed a firing frequency threshold (5 Hz) above which a long-lasting change in the Ca2+ content of somato-dendritic mitochondria was observed. These responses were reduced by blocking voltage-gated Ca2+ channels or the mitochondrial Ca2+ uniporter (using Ru360). Consistent with these findings, Ru360 profoundly enhanced the magnitude/duration of cytosolic Ca2+ signals only at firing frequencies above 5

Hz. Collectively, our results reveal that dramatic changes in mitochondrial [Ca2+] occur in situ in a non-pathological setting. Our findings suggest that the link between spike frequency and mitochondrial [Ca2+] changes could regulate both cellular energetics and cytosolic [Ca2+] signalling during heightened neuronal excitability.

2-B-36 A Putative Channel that Drives Spreading Depolarization evoked by Ischemia

R. David Andrew[1], Peter Gagolewicz[2]

[1]Queen's University, [2]Queen`s University

Ischemic neurons undergo spreading depolarization (SD) within minutes of heart failure, brain injury or focal stroke. Neurons can die within minutes. The current(s) driving SD remain unidentified. Czeh et al. (1993) showed that the SD macro-conductance is inward, cationic, non-selective and reverses near 0 mV. Like ischemic SD itself, this conductance resists blockers of standard voltage- and ligand-gated channels. In neocortical slices from adult rat, membrane patches from pyramidal neurons were voltage clamped during oxygen-glucose deprivation (OGD) at 35°C. Cell-attached (c-a) patches were bath superfused with blockers of Na, K, Ca, pannexin and glutamate-related channels, also included in the pipette. This silenced all spontaneous channel activity within 2 min. Within 5 min of OGD, novel channel opening commenced. The mean unitary current was 1.7 pA at holding potential (h)= -70 mV. Unitary event frequency increased, as did multiple channel openings. More positive h values reversed the unitary current near 0 mV, implicating a Na/K conductance. Channel slope conductance was ~28 pS based on unitary pA values from 23 neurons (h= -90 to 50 mV). The marine poison palytoxin (PLTX) binds the Na/K pump, converting it into an open Na/K channel and inducing SD in neocortical slices (10 nM in bath). C-a recordings with 1 pM PLTX blockers in the pipette opened a channel similar to OGD. Outside-out patch recordings comparing OGD and PLTX also revealed comparable channel opening. We propose that ischemia induces conversion of the Na/K pump into an open channel that generates SD.

2-B-37 Illuminating axon tension with a beta spectrin-based sensor in organotypic brain slices

Linda Dansereau[1], Dong Li[1], Marianna Kiraly[1], Daniel Madison[1], Miriam Goodman[1]

[1]Stanford University

Ultrasonic neuromodulation is a novel technique proposed as a therapeutic treatment of neurological disorders, though the mechanism of action is unclear. There is evidence that changes in membrane stress and activation of mechanosensitive ion channels are important components of the effect of ultrasound on neurons. To further study this effect we are developing a spectrin-based tension sensor that will enable measurement of cytoskeletal strain. Recently, a FRET-based tension-sensor module (TSM) was incorporated into C. elegans β-spectrin, UNC-70, showing the spectrin cytoskeleton is required for touch sensation (1). Given the high conservation of β-spectrin across species, we investigate whether the same sensor can be used to visualise cytoskeletal tension in mammalian neurons. Methods: The Unc70-TSM construct and associated controls were subcloned into the pcDNA3.1 vector and transfected into organotypic hippocampal slices prepared from P6 rats. Expression in neurons (MAP2), and localisation to the cytoskeleton (βII spectrin, βIV spectrin) was determined through immunofluorescence via confocal microscopy. Results: The expression pattern of Unc70-TSM is distinct from the cytosolic TSM control, and is similar to that of βII spectrin staining. Co-staining of Unc70-TSM transfected cells with β-spectrin antibodies indicates colocalisation. Conclusions: The C. elegans β-spectrin homolog is incorporated into the mammalian cytoskeleton. This will allow us to analyse changes in axonal tension through FRET imaging. (1) Kreig et al., 2014, doi:10.1038/ncb2915

2-C-38 Combining vibro-tactile P300 and Motor Imagery Brain-Computer Interface to assess and communicate with Locked-in Patients

Slav Dimov[1], Christoph Guger[1], Rossella Spataro[2], Alexander Heilinger[3], Woosang Cho[3], Rupert Ortner[3]

[1]g.tec neurotechnology USA, Inc., [2]University of Palermo, [3]g.tec medical engineering GmbH

With an increasing need to access and communicate locked-in syndrome (LIS) and complete locked-in syndrome (CLIS) patients, a visual independent brain-computer interface (BCI) system was developed. 9 LIS patients and 3 CLIS patients were assessed by three different modes of the system, vibrotactile stimulation with 2 vibro-stims (VT2), with 3 vibro-stims (VT3), and with motor imagery paradigms (MI). In VT2 mode, two vibro-stims were fixed on the left and right wrist separately, and the patient was asked to count the stimuli on the target side to elicit a P300 response. In VT3 mode, an additional vibro-stim was placed on the back, and in the MI mode, the patient was instructed to imagine either left or right-hand movement. VT3 and MI

modes were also used for simple yes or no questions. The patients achieved a mean accuracy of 76.6% in VT2, 63.1% in VT3, and 58.2% in MI after 2 training runs, 9 of 12 LIS patients could communicate with VT2 and VT3 (on average 8 of 10 questions answered correctly), and 3 of 12 patients could communicate with MI paradigm (4 of 5 questions answered correctly). 2 of the 3 CLIS patients could communicate with VT3 (70% and 90% accuracy respectively). It is the first study showing BCI-based communication with CLIS patients and was able to bring 9 of 12 patients to communicate with high accuracies using non-visual evoked potentials and motor imagery, more importantly, it was achieved within 20 min.

2-C-39 Structural Biomarkers of Parkinson's disease: Striatal sub-regional structural analysis with 3T MRI

Nole Hiebert[1], Ali Khan[2], Andrew Vo[3], Brian Wang[3], Adrian Owen[1], Penny MacDonald[2]

[1]Brain and Mind Institute/ Western University, [2]Western University, [3]University of Western Ontario

Parkinson's disease (PD) is a progressive disorder for which there are no reliable biomarkers. The aim of this study was to explore the potential of sub-regional analysis of the striatum to distinguish PD patients from controls as well as to track disease progression. Using a 3T MRI scanner, diffusion tensor and T1-weighted scans were repeatedly obtained on 16 PD patients and 13 matched healthy controls on two separate days. The striatum was parcellated into seven distinct sub-regions, guided by cortical regions to which they are reciprocally connected. Volume, surface-based morphometry, and connected white matter integrity (fractional anisotropy) were calculated for each striatal sub-region. Global structural measures of striatum were not significantly different between PD patients and controls (all $p > 0.85$). However, the caudal-motor striatum, the region first and most severely dopamine deprived, was significantly atrophied in PD patients compared to controls. Integrity of white matter cortico-striatal connections in sub-regions of the dorsal striatum (i.e., caudal motor, executive, parietal, and temporal) was reduced for PD patients relative to controls. Finally, volume of limbic striatum, the only striatal sub-region innervated by the later-degenerating ventral tegmental area, was sensitive to disease progression using both motor and cognitive indices. Structural measures of striatal sub-regions, segmented based on cortical-connectivity, provided a sensitive means for distinguishing PD patients from controls and for tracking disease progression.

2-C-40 Cell autonomous effects of Mecp2 mutation on spontaneous and nicotinic acetylcholine receptor evoked responses in medial prefrontal cortex layer V/VI pyramidal neurons in female Rett model mice

Azam Asgari[1], Jay Leung[1], Kerry R Delaney[1]

[1]University of Victoria

Dysfunction of the prefrontal cortex (PFC) is thought to play an important role in cognitive and behavioral deficits in neurodevelopmental disorders. Rett syndrome (RTT) is a neurodevelopmental disorder caused by mutation in the X-linked MECP2 gene. We aim to understand how lack of MeCP2 (MeCP2-) alters circuit function in the medial PFC with particular focus on MeCP2+/- females for which random X-inactivation produces a mosaic of MeCP2- and wild-type (WT; MeCP2+) neurons. We used whole-cell patch clamp to compare spontaneous synaptic and nAChR-evoked responses of MeCP2+ to MeCP2- neurons. Neuronal genotype in Mecp2+/- female slices was identified by presence or absence of expression of a WT-MeCP2-GFP fusion protein. MeCP2- pyramidal neurons in layer V (LV) and LVI of male null mice and LVI of Mecp2+/- female mice exhibit significant reductions in spontaneous excitatory (E) postsynaptic charge. For Mecp2+/- females inhibitory (I) synaptic charge in LVI MeCP2- neurons was the same as Mecp2+ but was increased in LVI of Mecp2-null male mice. A 1 sec. puff of ACh to LVI revealed significantly reduced direct AChR-currents in MeCP2- neurons in both male and female mice. The relative increase in frequency of E and I synaptic inputs evoked by 1 min bath applied ACh was similar in WT and MeCP2- male LV neurons but the increased frequency persisted for 10's of seconds in MeCP2- while adapting in WT. These studies demonstrate both cell autonomous (cell genotype specific) and sex specific effects of Mecp2 mutation in female mice on spontaneous E/I balance and AChR mediated responses.

2-C-41 Impaired homeostatic plasticity in YAC128 HD mouse cortical neurons rescued by pridopidine

Amy Smith-Dijak[1], Wissam Nassrallah[1], James Mackay[1], Geva Michal[2], Michael Hayden[1], Lynn Raymond[1]

[1]University of British Columbia, [2]Teva Pharmaceutical Industries Ltd

Homeostatic plasticity is a key mechanism for maintaining stability in brain circuits. By globally adjusting the strength while preserving relative weights of synapses, homeostatic synaptic scaling maintains neuronal activity in a physiological range, facilitating new learning and mental

flexibility, which are impaired early in Huntington disease (HD). Previous work in rodent cortical neurons shows that 48h treatment with tetrodotoxin (TTX) to block action potentials causes up-scaling of excitatory glutamatergic synapses via reduced activity-dependent release of Brain-Derived Neurotrophic Factor (BDNF). Since mutant huntingtin protein reduces BDNF release from cortical neurons, we hypothesized that this deficit in YAC128 impairs scaling, and that pridopidine, which upregulates BDNF signalling in rodents (Geva, HMG 25:3975, 2016), could rescue it. Here, we recorded miniature excitatory postsynaptic currents (mEPSCs) from YAC128 and wild-type (WT) mouse cortical cultures after 48h TTX vs. vehicle control treatment. WT cortical neurons responded to action potential silencing with increased frequency and amplitude of mEPSCs, while YAC128 did not. Pre-treatment for 48h with 1μM pridopidine before TTX exposure restored synaptic up-scaling in YAC128 neurons. Our data also support a role for BDNF in synaptic up-scaling in this model system, as well as a role for the sigma-1 receptor. These results shed new light on mechanisms by which pridopidine may slow decline in functional capacity in HD and potentially ameliorate cognitive deficits associated with early stage disease.

2-C-42 Rescue of motor deficits in an ARSACS mouse model by a mitochondria-targeted antioxidant

Brenda Toscano[1], Jeanette Hui[1], Sasha McDowell[1], Anne McKinney[1], Alanna Watt[1]

[1]McGill University

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is an early onset neurodegenerative disease characterized by progressive ataxia and cerebellum degeneration. ARSACS is caused by mutations in the SACS gene encoding the protein sacsin, which is proposed to have roles in protein chaperoning, the ubiquitin-proteasome system and mitochondria functions. Both ARSACS patients and a mouse model (SACS-/-) show altered mitochondrial shape and motility and metabolic processing functions in several cell types. In SACS-/- mice, these changes are accompanied by alterations in Purkinje cell firing output and synaptic input. It has been proposed that altered mitochondria functions may be an underlying cause of Purkinje cells pathophysiology. With this in mind, we investigated whether treatment with the mitochondria-targeted anti-oxidant MitoQ could improve motor performance in Sacs-/- mice. We administered MitoQ in drinking water for 12 weeks and assessed motor coordination with a Rotarod apparatus and balance beam assay in MitoQ- and sham-treated Sacs-/- mice. We then performed loose cell-attached recordings from Purkinje cells and

quantified Purkinje cell death for each experimental group. Our results show that MitoQ improves motor behaviour in Sacs-/- mice, but that this rescue occurs independent of Purkinje cell deficits. These findings suggest that MitoQ represents a potential treatment to ameliorate motor dysfunctions in ARSACS patients, although the mechanism by which it acts is still under investigation.

2-C-43 Mild Na+/K+ ATPase inhibition by ouabain facilitates tissue swelling during spreading depolarization

Yanqi Liu[1], Brian MacVicar[1]

[1]University of British Columbia

Spreading depolarization (SD) is a transient wave of neuronal depolarization propagating across the neocortex followed by periods of electrical silence. During SD, tissue swelling occurs and there are changes in tissue light scattering. SD is implicated in disorders such as acute brain injuries and migraine aura. SD is thought to be innocuous or detrimental (expands infarct volume) depending on the situation. In attempting to delineate the mechanisms determining SD outcomes, we investigated the effects of low concentrations of ouabain, the Na+/K+ ATPase inhibitor, to mimic possible effects of metabolic challenge on properties of SD. Nanomolar concentrations of ouabain were used to mimic situations during stroke where reduced activity of the Na+/K+ ATPase may occur due to impaired ATP production in low O2-glucose conditions. We hypothesized that ouabain would increase the magnitude and duration of both tissue and neuronal swelling as well as causing alterations in the optical signals during SD. We used two-photon imaging to monitor cortical tissue area and neuronal cross sectional-area in brain slices. In addition, SD onset, wave front characteristics, as well as tissue light transmittance were obtained and analyzed. In the presence of ouabain, there is a significant dose-dependent increase in cortical tissue swelling during SD. We are currently measuring cross-sectional area changes of single neurons during SD with and without ouabain. Identifying factors determining SD outcomes will help in identifying therapeutic strategies in SD related disorders.

2-C-44 Myelin Water Changes in Normal Appearing White Matter Correspond with Postural Tremor in Parkinson's Disease

Jowon Laura Kim[1], Tobias Baumeister[1], Martin McKeown[1]

[1]University of British Columbia

Background: Rest tremor is characteristic of Parkinson's disease (PD), but postural and kinetic tremor can often be seen. White matter is typically considered unaffected in PD, but newer magnetic resonance sequences, such as Myelin Water Fraction (MWF), are beginning to suggest that myelin may be affected. Methods: Twenty-four PD subjects were scanned and clinically assessed at the movement disorders clinic of the Pacific Parkinson's Research Centre (UBC). Twenty white matter Regions of Interest (ROIs) were selected using the JHU atlas. A multivariate statistical approach, Canonical Correlation Analysis (CCA), was used to determine the association between tremor scores from the Unified Parkinson's Disease Rating Scale (UPDRS) and the mean MWF values in the different ROIs. A Leave-One-Out Cross Validation approach was used to determine which tremor scores and which white matter ROIs had the greatest influence on the correlation. Results: We found a correlation of 0.82 (p=0.0077) between UPDRS tremor scores and myelin features. Postural and kinetic tremor were most strongly associated with MWF scores in ROIs. The ROIs most strongly associated with tremor were the left and right corticospinal tracts, left cingulum hippocampus, left and right superior longitudinal fasciculi, and right thalamic radiation. Conclusion: Our results are consistent with prior studies suggesting the severity of tremor in PD is not exclusively due to basal ganglia dysfunction. Specifically, postural and kinetic tremor may be associated with widespread white matter dysfunction in PD.

2-C-45 D-lysergic acid diethylamide (LSD) reverses depressive-like behavior and serotonergic (5-HT) neurotransmission impairments in a murine model of chronic stress.

Danilo De Gregorio[1], Justine Enns[1], Luca Posa[1], Martha Lopez-Canul[1], Gabriella Gobbi[1]

[1]McGill University

D-lysergic diethylamide acid (LSD) is a hallucinogen which has recently gained popularity due to clinical evidences reporting mood-enhancing properties but its effect on serotonergic system has not been examined in animal models of depression. Using a chronic stress (CS) model of depression, our hypothesis is that low doses of LSD could reverse depressive and anxiety-like symptoms and increase the serotonin (5-HT) activity in the Dorsal Raphe (DR), area involved in depression. Methods: The CS paradigm: 8-week old male C57BL/6J mice were placed in restrainers for 2 hours per day, over 14 days. Control mice (CTL) remained undisturbed in their cages. From 7th to 14th day of stress, both CTL and CS mice received LSD (30 µg/kg/day, s.c.) or vehicle (veh); on the 15th day after the CS, the groups of mice were tested separately. In vivo extracellular recordings of 5-HT DR neurons were employed. Behavioral tests such as Open Field

(OF), Forced Swim (FS) and Novelty Suppressed Feeding (NSF) were performed. Results: CS mice showed decreased activity of 5-HT DRN neurons compared to CTL. LSD restored firing to CTL levels. In OF, CS mice spent less time in the center, compared to CTL. Frequency of the entrance in center was also reduced. LSD normalized these parameters to CTL levels. CS mice showed increased immobility time compared to CTL mice in the FS, normalized by the LSD treatment. In NSF, LSD reduced the latency to feed in CS mice, increased after 14 days of stress. Conclusion: This study shows that short-term treatment with LSD modulates mood through 5-HT neurotransmission.

2-C-46 Characterization of hiPSC derived striatal neurons to study Huntington disease pathology.

Sakthikumar Mathivanan[1], Sergey Akimov[2], Christopher A Ross[2], Lynn Raymond[1]

[1]University Of British Columbia, [2]John Hopkins University School Of Medicine

Huntington disease (HD) is a fatal inherited neurodegenerative disorder caused by expansion of CAG repeats >35 in the HTT gene, encoding expanded polyglutamine (Q) in the huntingtin protein and resulting in striatal neuronal dysfunction and death. To study the pathology of human HD, we characterized neurons derived from human immortalized striatal neuronal precursor cells (NPCs). For the differentiation phase, we used BrainPhys medium (STEM Cell Technologies), which we found optimized maturation of NPCs to functional neurons. We observed that cells from both control (33Q) and HD (180Q) lines expressed striatal neuronal markers MAP2, DARPP32 and VGAT. Functional analysis of these differentiated neurons by whole-cell recording confirmed expression of voltage-gated Na+ and K+ channels. Furthermore, Na+ currents in both control and HD cells were sensitive to 0.3μM Tetrodotoxin (TTX), suggesting similar populations of TTX-sensitive Na+ channels. Measurement of intrinsic membrane properties (resistance and capacitance) revealed no significant differences between control and HD cells, and no synaptic events were observed. Resting membrane potentials of these neurons were relatively depolarized. Nevertheless, a rebound action potential was observed following injection of a hyperpolarizing current in both cell lines, a characteristic feature of striatal medium spiny neurons. These preliminary data support the principle of deriving striatal neurons from human immortalized striatal precursor cells, which could serve as a platform to study the mechanism of HD pathology.

2-C-47 CHIMERA repetitive mild traumatic brain injury induces long-term pathological and PTSD-like changes in APP/PS1 mice

Wai Hang Cheng[1], Kris Martens[1], Sophie Stukas[1], Emily Button[1], Anna Wilkinson[1], Asma Bashir[1], Carlos Barron[1], Peter Cripton[1], Cheryl Wellington[1]

[1]University of British Columbia

The annual incidence of traumatic brain injury (TBI) is over 2.5 million in US, with over 3 million people living with residual problems. Moderate and severe TBI survivors have high rates of long-term disability and neurodegeneration. Though symptoms of mild TBI (mTBI, the most common form of TBI) usually resolve within weeks, some patients may develop "post-concussive syndrome" and present long-term complications. Repetitive mTBI is also linked to chronic traumatic encephalopathy, a neurodegenerative condition characterized by perivascular tau deposits at sulcal, and possible amyloid deposition (50%), years after injury. We recently reported the acute outcomes of two mTBI (0.5J, 24 hr apart) in the APP/PS1 amyloidogenic mouse model (6-mo or 13-mo), using the Closed-Head Injury Model of Engineered Rotational Acceleration (CHIMERA). In this study, we used the same mTBI paradigm to injure APP/PS1 and WT mice at 6-mo, and assessed the long-term behavioral, histological, and biochemical outcomes up to 8-mo post-TBI. Both APP/PS1 and WT mice with TBI had white matter microgliosis (Iba1) and axonal injury (Silver) up to 8-mo post-TBI. They also showed reduced anxiety-like behavior (Elevated plus maze). Interestingly, long-term fear memory (passive avoidance) was only chronically intensified in APP/PS1-TBI mice, suggesting post-traumatic stress disorder. In summary, two mild TBI are sufficient to induce long-term neuropathologies up to 8-mo post-injury. Moreover, TBI may exacerbate chronic cognitive deficits deficits to a greater extent in mice developing amyloid deposition.

2-C-48 The impact of methylenetetrahydrofolate reductase (MTHFR) deficiency in a paraquat mouse model of Parkinson's disease

Lauren Murray[1], Nafisa Jadavji[1], Chris Rudyk[1], Shawn Hayley[1], Patrice Smith[1]

[1]Carleton University

Parkinson's disease (PD) is a common neurodegenerative disorder. Environmental toxicants such as paraquat have been linked to the dopaminergic (DA) cell death seen within the substantia nigra (SNc), although the cause remains unknown. Several risk factors have been proposed, including nutrition, with metabolism of the B-vitamin folic acid appearing to be particularly

important. For example, individuals with a polymorphism in the enzyme methylenetetrahydrofolate reductase (MTHFR) have increased risk for PD, however, the mechanism is not well understood. Using a mouse model that mimics the human MTHFR polymorphism, the aim of this study was to determine whether MTHFR deficiency leads to enhanced degeneration in a toxicant (paraquat) mouse model of PD. Male 3-month-old Mthfr+/+ and Mthfr+/- mice received 6 injections of paraquat or saline, after which motor and memory functioning were tested. Interestingly, Mthfr+/- mice were especially vulnerable to paraquat, as they showed motor impairment compared to Mthfr+/+ mice on the rotarod task. In the 2-trial y-maze, a trend for memory impairment was observed in the paraquat treated Mthfr+/- mice. Within the SNc, there were no significant differences in DA neuronal numbers or antioxidant activity. However, we observed increased antioxidant activity within the dorsal striatum of paraquat treated Mthfr+/- mice. These results suggest there may be enhanced vulnerability to paraquat-induced damage as a result of MTHFR deficiency through changes in antioxidant activity within the dorsal striatum.

2-C-49 A Comparison of Neural Circuitry in Older Persons with Late-Life Depression, Mild Cognitive Impairment, Alzheimer's Dementia, or Normal Cognition

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

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

Objective: The pathways linking late-life depression (LLD), mild cognitive impairment (MCI), and Alzheimer's Dementia (AD) are complex and bidirectional. We investigated neural circuitry associated with the executive control network and the cortico-limbic network because changes in both networks have been implicated in these disorders. Methods: T1-weighted and diffusion tensor imaging scans for 282 participants from five groups: history of major depression (LLD;n=43), LLD+MCI(n=43), MCI(n=122), AD(n=39), and aging controls(n=35) were acquired using the same acquisition sequences on a 3T scanner. We compared cortical thickness, subcortical volumes, white matter fractional anisotropy (FA), and mean diffusivity (MD) in the executive control (EC) and cortico-limbic (CL) networks across the five groups using an ANOVA and GLM model (Age*Diagnosis, with sex as a covariate). Results: The AD group demonstrated

significant decreases in cortical thickness, subcortical volume, and FA (with increases in MD) in all networks. The other four groups did not differ significantly in their hippocampal volumes, entorhinal and frontoparietal cortex thickness, and FA or MD of the cingulum bundle and genu of the corpus callosum. Conclusion: AD was associated with deleterious changes in EC and CL networks. By contrast, the four other groups did not differ significantly. We attribute this surprising finding to the heterogeneity among our participants. Using more sophisticated measures of brain network architecture or further clinical subtyping might uncover additional differences in brain circuitry.

2-C-50 Isolation of plasma high-density lipoproteins by differing methods reveals multiple distinct protective effects on brain endothelial cells against amyloid beta

Emily Button[1], Jerome Robert[1], Megan Gilmour[1], Harleen Cheema[1], Cheryl Wellington[1]

[1]University of British Columbia

Alzheimer's disease (AD) is characterized by amyloid beta plaques and neurofibrillary tangles however cerebrovascular dysfunction also occurs in most cases. A potential therapeutic target to improve vascular health is high-density lipoprotein (HDL). HDL is a plasma lipid carrier that can promote vascular health in peripheral arteries and has protective epidemiological associations with AD. We have previously shown that HDL can maintain cerebrovascular health using 2D and 3D in vitro models by suppressing inflammation, inducing endothelial nitric oxide production, and reducing the deposition of amyloid beta within the vascular wall. Here we provide evidence that these vasoprotective effects occur through multiple distinct pathways. We compared the functional abilities of HDL isolated from human plasma by methods of ultracentrifugation and precipitation. The method by which HDL is isolated can affect its composition, specifically ultracentrifugation methods remove all non-HDL proteins while precipitation methods produce an isolate containing an abundance of albumin. We found that HDL isolated by both methods effectively reduced amyloid beta vascular accumulation but only HDL isolated by ultracentrifugation suppressed brain endothelial cell inflammation and induced nitric oxide production. The discrepancy in the functional abilities of HDL isolated by different methods suggests that HDL acts through multiple pathways to promote brain vascular health. Therefore, there are several distinct, protective functions of HDL to be explored therapeutically in the context of AD.

2-C-51 Murine overexpression of the LRRK2 G2019S mutation is implicated in stress response and neuroplastic effects following sub-chronic paraquat treatment

Zachary Dwyer[1], Christopher Rudyk[1], Ashley Thompson[1], Shawn Hayley[1]

[1]Carleton University

Parkinson's disease (PD) is characterised by a loss of dopamine producing neurons in the substantia nigra. Although PD's hallmark symptoms are motor dysfunctions, several non-motor symptoms are also often evident emerging prior to or concurrently to diagnoses. These include depression and anxiety amongst others. Several possible mechanisms that could contribute to this wide range of symptoms have been proposed of which chronic, microglia-driven inflammation is of particular importance. In this regard, Leucine-Rich-Repeat Kinase 2 (LRRK2) has been strongly linked to both inflammation and PD. The most common mutation, Gly-2019S-Ser (G2019S), accounts for up to 10% of familial and 1.5% of sporadic PD cases. In order to investigate the role of LRRK2, we sub-chronically injected 10mg/kg of the oxidative stressor, paraquat (a common pesticide that has been repeatedly linked to PD) in wild type and G2019S overexpressing mice at eight months of age. We found no augmented toxicity in G2019S overexpressors, however, these mice did display exaggerated corticosterone, along with alterations in brain derived neurotrophic factor (BDNF) and the glucocorticoid receptor (GR). Thus, it appears that G2019S overexpression in these animals might selectively alter stressor responses involving hormonal and neuroplastic factors.

2-C-52 Mechanism of pannexin channel activation in Alzheimer's disease

Chetan Patil[1], Natalie Lavine[1], Michael Jackson[1]

[1]The University of Manitoba

Loss of Ca2+ homeostasis is one of the leading hypotheses underlying the pathology of Alzheimer's disease. In this regard, amyloid-β oligomers (AβOs) have been suggested to provoke aberrant activation of Ca2+ permeable NMDA receptor (NMDARs). Previous studies have shown that, overactivation of NMDARs provokes pannexin (Panx1) channel activation, however the signaling cascade involved have not been precisely identified. Hippocampal enriched neuronal cultures from CD1 mice were used for electrophysiological recordings. NMDA application for duration of 5 min reliably evoked Panx1 currents which were blocked by Lanthanum. The role of NMDAR and its subunits (NR2A/2B) in generating Panx1 currents was confirmed with use of specific antagonists. Blocking NMDAR, specifically the NR2A subunit inhibited generation of

Panx1 currents. The role of ryanodine receptors (RyR), activated downstream of NMDAR was confirmed using S107 (blocker) and 4-CMC (agonist). Modulating the activity of RyR had no effect on NMDA evoked Panx1 currents. Previous data from Jackson lab has shown that, dantrolene [blocks RyR and IP3R] blocked Panx1 currents. Future experiments are targeted to study the synergistic role of RyRs and IP3Rs in Panx1 activation. The effect of AβOs on Panx1 channel was determined with 24-72 hrs of treatment. Interestingly, the Panx1 channel activity was sensitized within 72 hrs of treatment. Investigating the signaling cascade for Panx1 activation may influence discovery of potential therapeutic targets for impeding detrimental effects of AβOs.

2-C-53 Effect of unilateral Endothelin-1 injections into the medial prefrontal cortex and/or nucleus accumbens on depressive- and anxiety-like behaviour in the rat

Denise Happ[1], R. Andrew Tasker[1], Gregers Wegener[2]

[1]University of Prince Edward Island, [2]Aarhus University

Post-stroke depression (PSD) and post-stroke anxiety (PSA) are usually undertreated and many cases may remain undiagnosed. This indicates a need for a better understanding of the underlying mechanisms and improved treatments. Current animal models of PSD and PSA, using middle cerebral artery occlusion, are associated with motor deficits that can interfere with behavioural tests of depression and anxiety. In the present study, we investigated whether microinjections of the vasoconstrictor endothelin-1 (ET-1) in the nucleus accumbens (NAc) and/or medial prefrontal cortex (mPFC) altered depressive- and anxiety-like behaviour in rats. ET-1 (400 pmol)(or vehicle control) was injected into the left NAc and/or mPFC of adult male Sprague-Dawley rats (300 - 380 g; n=10 per group) using stereotaxic surgery under isoflurane anesthesia. All rats received a single injection of buprenorphine for post-operative analgesia. Behaviour was evaluated at 2 and 6 weeks post stroke using standard tests for locomotion (Open Field), anxiety (Elevated Plus Maze), and depression (Forced Swim Test). At this time data acquisition is on-going and experimenter blind, however, in a pilot study ET-1 injections into the left mPFC alone caused increased anxiety, with no effect on motor function or depressive-like behaviour. We expect that unilateral lesions of the NA and mPFC will increase both anxiety- and depressive-like behaviour without affecting motor function. Supported by Aarhus University.

2-C-54 Mismatch negativity-indexed auditory change detection of speech sounds in early and chronic schizophrenia

Derek Fisher[1], Erica Rudolph[2], Emma Ells[1], Verner Knott[3], Alain Labelle[3], Philip Tibbo[4]

[1]Mount Saint Vincent University, [2]Saint Mary's University, [3]The Royal's Institute of Mental Health Research, [4]Dalhousie University

Auditory change detection, as indexed by the EEG-derived mismatch negativity, has been demonstrated to be dysfunctional in chronic schizophrenia using both pure-tone and speech (phoneme) sounds. It is unclear, however, whether reduced MMN amplitudes to speech sound deviants are observed within the first 5 years of the illness as no study to date has reported findings in this population. The present study investigated MMNs elicited by across-vowel (phoneme) change in early schizophrenia (ESZ; Experiment 1) as well as chronic schizophrenia (CSZ; Experiment 2). In both experiments, clinical and control participants were presented the Finnish phoneme /e/ (standard; P = .85) and the Finnish phoneme /ö/ (deviant; P = .15) within an oddball paradigm. In experiment 1 we report significantly reduced MMN amplitudes in CSZ relative to HCs, but no differences were found when comparing ESZ and HC in experiment 2. Follow-up of these findings showed smaller MMN amplitudes in CSZ participants compared to ESZ participants. These findings suggest that early detection of phonetic change is impaired in chronic populations, but not in populations early in the progression of the illness. That MMN reductions only emerged in patients with a longer course of illness suggests a dynamic change in the preconscious processing of language over time in schizophrenia.

2-C-55 Medulloblastoma secreted ligands disrupt normal neural stem cell function

Alexander Gont[1], Freda Miller[2], David Kaplan[1]

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

Long-term cognitive impairments are frequently observed in pediatric brain cancer survivors. While these impairments were initially thought to arise as a consequence of irradiation and treatment, recent reports suggest a link to tumour-specific mechanisms. We therefore hypothesised that pediatric brain tumours including medulloblastomas (MB) can directly affect neural stem cell (NSC)/precursor (NPC) function by secreting bioactive factors. Cell lines representing the spectrum of molecular subgroups of MB were cultured and conditioned media (CM) was collected. CM from group-3 MB lines increased the self-renewal of NSCs, while CM from the Shh-group MB lines resulted in increased STAT3 activation, differentiation, and

decreased self-renewal. CM treatment also promoted glial differentiation of NPCs. To identify the ligands secreted by MB cells that perturb NSC biology, an in silico interaction model was used to extract ligands from MB microarray data and predict which will bind receptors expressed by P7 NSCs. Ligands were validated by antibody arrays. Using recombinant proteins, we identified several that regulated NSC self-renewal and are assessing their in vivo effects by intraventricular injection. To determine the effect of MB tumours on NSC function in vivo, we established subcutaneous MB xenografts. Mice harboring MB tumours had fewer proliferating NSCs in the SVZ than control mice suggesting an exhaustion of the NSC pool. Overall, this work demonstrates that MB cells secrete ligands that perturb NSC function and potentially neurodevelopment and cognitive function.

2-C-56 Contribution of Pannexin-1 activation to amyloid-β induced synaptic dysfunction

Albert Yeung[1], Yufeng Xie[2], Natalie Lavine[3], Michael Jackson[3]

[1]University of Manitoba, [2]Western University, [3]The University of Manitoba

Introduction: Soluble amyloid-beta oligomers (AβOs) induce deficits in synaptic plasticity and the loss of excitatory synapses. Evidence points to the dysregulation of NMDA receptor signalling cascades in this process. Pannexin-1 (Panx1) is a large-pore non-selective ion channel which can be activated downstream of NMDA receptors. Panx1 mediates large inward calcium currents and the efflux of intracellular metabolites such as ATP. We hypothesize that the pathological activation of Panx1 leads to aberrant calcium signalling and contributes to synaptic degeneration in Alzheimer's Disease. Methods: Acute hippocampal slices from Panx1 KO and WT mice were pre-treated with AβOs and long-term potentiation (LTP) was recorded. To assess prolonged synaptic degeneration, primary hippocampal neurons from Panx1 KO and WT were treated with AβOs. Synaptic NMDA receptors were stimulated with bicuculline and 4-aminopyridine. Changes in PSD-95 and synaptophysin expression was assessed with Western Blot. The activation of Panx1 was quantified by YoPro-1 dye flux. Results: Preliminary data show a rescue of LTP in Panx1 KO slices pre-treated with AβOs. In cultured neurons, PSD-95 and synaptophysin levels were reduced with AβO treatment, and the loss of these synaptic markers was attenuated in Panx1 KO neurons. There was a greater increase in Panx1 activation in stimulated neurons treated with AβOs. Conclusion: Our data suggest a role of Panx1 in AβO induced synaptic dysfunction. Further experiments will explore the underlying mechanisms mediating these effects.

2-C-57 Investigating an Alpha-Synuclein Binding Aptamer as a Potential Treatment Avenue to Prevent Protein Fibril Formation in Parkinson's Disease

Katelyn Ventura[1], Erin McConnell[1], Joshua Callahan[1], Vernon Hunt[1], Anna Koudrina[1], Maria DeRosa[1], Matthew Holahan[1]

[1]Carleton University

A key component of the neurodegenerative processes underlying Parkinson's Disease (PD) is the aggregation of alpha-synuclein (α-Syn). One current hypothesis is that misfolded native or mutant α-Syn protein dimers become oligomers and can form insoluble fibrils eventually leading to aggregation into inclusions. These fibrils and inclusions have been found to trigger apoptotic and other toxic signals leading to neuron death. The ability to prevent this aggregation during the disease process would have enormous potential for slowing the neurodegenerative cascade in PD. Using bionanotechnology strategies, we have sought to determine whether a DNA aptamer, targeted to bind to alpha-synuclein monomers, can inhibit protein aggregation and reduce Parkinson's-related neurodegeneration. Specifically, we have identified a DNA aptamer that can recognize, bind, and block the aggregation of α-Syn protein. Our DNA aptamer selectively bound to the α-Syn monomer and prevented α-Syn fibril formation in vitro. Next, we assessed the ability of the α-Syn binding aptamer in vivo in transgenic mice expressing the human A53T variant of α-Syn. We examined the colocalization of the anti-alpha-synuclein (phosphor S129) antibody and Cy3.5 labelled α-Syn aptamer on ex vivo tissue slices using fluorescent microscopy. Our results suggest that we have been successful at targeting and binding to α-Syn both in vitro and in vivo. The ability to inhibit protein aggregation with an exogenous treatment during aging would be a key strategy in studying and potentially slowing the neurodegenerative process in PD.

2-C-58 Effect of Low Field Magnetic Stimulation on Restoring Neuronal and Glial Function Against 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine Induced Parkinson?s Disease Mouse Model

Sathiya Sekar[1], Yanbo Zhang[1], Changiz Taghibiglou[1]

[1]University of Saskatchewan

Parkinson's disease (PD) is a neurodegenerative disorder affecting motor and cognitive abnormalities. Recently, researchers showed that transcranial magnetic stimulation (TMS)

improves cognitive and motor functions in PD patients. Low-field magnetic stimulation (LFMS) is a new non-invasive TMS technique that generates deep brain magnetic stimulation. In the present study, the effect of LFMS on neuronal and glial activities, in turn motor function in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced PD mouse model was investigated. LFMS treated MPTP mice improved motor function compared to vehicle treated MPTP mice, as evidenced by stride length, beam walk, rota rod and open field tests. Further, LFMS treated mice showed significant increase in tyrosine hydroxylase (TH) and decrease in microglial marker (IBA1) levels when compared to vehicle treated MPTP mice, whilst no difference in astroglial marker (GFAP) level was observed between them. In addition, apoptotic marker like caspase 3 and inflammatory markers like TNFα and IL-1β levels were found to be ameliorated in LFMS treated MPTP mice brain compared to vehicle treated MPTP mice. The results obtained from the study clearly reveal the unswerving involvement of LFMS in restoring neuronal and glial activities, in turn motor functions in MPTP intoxicated mice. Thus, we suggest that LFMS may serve as the better therapeutic intervention in the treatment of PD. Further studies may warrant to clearly elucidate the underlying molecular mechanisms of LFMS in protecting dopaminergic neurons against PD pathogenesis.

2-C-59 Loss of Activating Transcription Factor 3 function diminishes the intrinsic regenerative response of peripheral nerves

Seth Holland[1], Ana Maria Oproescu[1], Matt Ramer[1]

[1]University of British Columbia

In the peripheral nervous system (PNS) injured neurons have the capacity to regenerate and restore function. This is unlike injury to the central nervous system (CNS) where regeneration is absent. Understanding the intracellular mechanisms that allow for regeneration in the PNS could provide valuable insights into why the CNS does not regenerate. Activating Transcription Factor 3 (ATF3) has been identified as a likely contributor to regeneration in the PNS. Currently no conclusive evidence exists to prove that a lack of ATF3 function diminishes regeneration. Using a transgenic mouse line, that has a non-functional allele of the ATF3 gene, we tested for differential regenerative capacity of wildtype, heterozygote, and homozygote mice after a sciatic nerve crush. In behavioral (response to toe pinch and grasping ability) and electromyographical assays we found significantly reduced functional regeneration in the homozygous mutants compared to the wildtype mice. A statistically-significant trend indicated a gene dosing effect when heterozygotes were included in analyses. Histological assays revealed aberrant

neuromuscular junction morphology in the ipsilateral muscle of the homozygous group when compared to the wildtype group. To follow up on these findings we will present data assessing axonal regeneration differences along the sciatic nerve two days after crush, and assaying reinnervation densities in the target tissue at later time points. These results provide compelling evidence that a loss of ATF3 function diminishes the regenerative response after PNS injury.

2-C-60 Inflammation in the gut of a new progressive model of Parkinson's disease

Joyce Sze Tung Lam[1], Geoffrey Ching[2], Daniel Kim[2], Jupjeet Sandhu[2], John O'Kusky[2], Doris Doudet[2]

[1]University of British Columbia & Pacific Parkinson's Research Centre, [2]University of British Columbia

Pathophysiology of the gastrointestinal tract is being explored as a means to diagnose and to measure the progression of Parkinson's Disease (PD). While the presence of Lewy bodies is seen as the primary marker of neurodegenerative disease-related gut pathophysiology, recent publications theorize that gut inflammation may also serve as a reliable indicator and a precipitating condition of PD (1). To explore the hypothesis that gut inflammation is a reliable indicator of PD, we ran a small pilot study: the gut of 13 experimental BSSG-induced PD rats (a novel progressive rodent model of PD (3)) and of 11 control rats were paraffinized, sliced, and stained using an anti-CD68 primary antibody and a goat anti-mouse secondary antibody. Preliminary results showed that an elevated inflammation was present in the gut submucosa of 12 experimental rats, versus only 4 out of 11 control rats. These data support further exploration of increased inflammation of gut submucosa in PD as well as in this novel progressive rodent model of PD. Further experiments to evaluate the colonic colocalization of α-synuclein aggregates with CD68 in the BSSG model are ongoing in larger sub-groups, and preliminary analyses show similar distribution patterns. Our data support the hypothesis that gut submucosa inflammation is indicative of PD development as much as brain inflammation. This is the first step to mapping the progression of inflammation in the gut along the timeline of the development of other pathophysiological symptoms. 1) Houser & Tansey, Parkinson's Disease, 2017 2) VK et al. PLOS One, 2015

2-C-61 Altered coordination among functional networks underlying semantic association in schizophrenia

Meighen Roes[1], Todd Woodward[1]

[1]University of British Columbia

Schizophrenia affects functional connectivity within brain networks and is associated with abnormalities in the extent of activation and suppression of language and responding networks, respectively. Impairment in controlled semantic association is a central feature of schizophrenia; the current study investigated the neural correlates of this deficit from the perspective of network-level interactions. Published fMRI data were used to examine the coordination of 3 functional brain networks engaged by a semantic integration task: two configurations of the salience network (responding and visual attention networks), and a language network in which coordinated activity was reduced in schizophrenia patients relative to healthy controls for distantly related word pairs. Principal component analysis (PCA) of patients' (n = 30) and controls' (n=28) estimated hemodynamic response indicated that the dominant associations among networks over the course of task differed for controls versus patients. In patients, hypoactivation of the language network was related to attenuated suppression of the responding network. This pattern correlated with poorer semantic association performance (reaction time, accuracy) and increased severity of reality distortion symptoms. This study uses a novel method to investigate cognitive impairment from the perspective of network-level interactions. Our findings suggest that the semantic association and reality distortion difficulties present in schizophrenia are related to inefficient coordination of neural resources among functional networks.

2-C-62 MicroRNA-RNA interactions within a pain-centered EAE mouse model: an unbiased predictive computational approach utilizing Next Generation Sequencing

Timo Friedman[1], Muhammad Saad Yousuf[1], Ana Cantuneanu[1], Bradley Kerr[1]

[1]University of Alberta

MicroRNA (miR) are short non-coding RNA regulatory molecules characterized by their ability to interfere with the translation process of RNA. Experimental autoimmune encephalomyelitis (EAE) is an inducible disease state with widespread pathway dysregulation at the protein and RNA level, including immune and inflammatory pathways. EAE is used for its similarities to Multiple Sclerosis (MS), as it mimics many aspects of motor disturbance in the disease, but also the heterogeneous pain syndromes across individuals. Although miRs have been studied in EAE, their role in tissues of the PNS is poorly understood. As the pain experienced by both MS

patients and EAE mice may arise in the periphery, we examined the pattern of miR expression in the dorsal root ganglion (DRG) of mice with EAE. We collected DRG samples from male and female mice with EAE that exhibited signs of pain hypersensitivity or not, as well non-disease controls. The samples were purified for both miR and RNA and sequenced by Next Generation Sequencing. RNA and miR statistically differing between groups were queried through online pathway databases for potential biological functions or theoretical RNA targets respectively. We have begun to validate miR-30a/d as it was strongly downregulated in our female cohort, but not male mice with pain. We have confirmed the upregulation of predicted miR-30 targets such as Stau1 and Magt1, providing evidence of our microarray's validity. In female mice, miR-30a/d may have a role in the induction of pain, although its specific function is still being investigated.

2-C-63 Focused ultrasound (FUS) enhancement of intranasal delivery of GDNF DNA nanoparticles to the rat brain

Amirah Aly[1], Tao Sun[2], Yongzhi Zhang[2], Ozge Sesenoglu-Laird[3], Linas Padegimas[3], Mark Cooper[3], Nathan McDannold[2], Barbara Wasczak[1]

[1]Northeastern University, [2]Harvard Medical School/Brigham and Women's Hospital, [3]Copernicus Therapeutics

Intranasal administration is a non-invasive means of circumventing the blood-brain barrier (BBB). We have previously shown that intranasal delivery of PEGylated lysine 30-mer compacted plasmid DNA nanoparticles encoding GDNF (pGDNF NPs), developed by Copernicus Therapeutics, can transfect brain cells in vivo, induce transgene expression, and provide neuroprotection in the rat 6-hydroxydopamine model of Parkinson's disease. We have also shown that transgene expression occurs primarily in cells abluminal to the vasculature, presumably pericytes. Focused ultrasound is a means of transiently disrupting the BBB to localize delivery of biomolecules to specific brain regions. Since the intranasal route provides no inherent means of targeting, we sought to determine if combining FUS with intranasal pGDNF NPs could enhance their delivery to the sonicated regions. Two sites, the right forebrain and midbrain, were sonicated before and after intranasal administration of the NPs. One week later, transgene expression in the brain was assessed by ELISA and DL-IHC. FUS-mediated disruption of the BBB shifted the distribution of transgene expression to the sonicated regions relative to the unsonicated side. At the sonication sites, large numbers of cells other than pericytes were transfected and located deeper in the parenchyma than at non-sonicated sites. These results demonstrate that FUS combined with intranasal administration of our DNA NPs increases

delivery to the sonicated brain areas, improves tissue penetration, and locally enriches transgene expression at target brain regions.

2-C-64 Role of Palmitoylation of huntingtin (HTT) on the HTT post-translational modification (PTM) network in Huntington disease

Fanny Lemarie[1], Shaun Sanders[1], Dale Martin[1], Michael Hayden[1]

[1]University of British Columbia

Huntington disease (HD) is an incurable neurodegenerative disorder characterized by motor, cognitive and psychiatric dysfunctions. It is caused by a polyglutamine (polyQ) repeat expansion in huntingtin (HTT), a scaffold protein involved in various functions including vesicle and organelle trafficking. HTT protein-protein interaction, localization and clearance are regulated by post-translational modifications (PTMs) such as phosphorylation, proteolytic cleavage and palmitoylation. The polyQ expansion disturbs many PTMs in HD, contributing to mutant HTT (mHTT) toxicity. Some HTT PTMs (phosphorylation at S421, D586 cleavage) are critical for HD pathogenesis, thus normalizing their levels could alleviate HD phenotypes in animal models. Palmitoylation is a common lipid modification in the brain which regulates diverse aspects of neuronal protein trafficking and function. HTT is palmitoylated at cysteine 214. Interestingly, mHTT is less palmitoylated in HD mouse models and this contributes to aggregation and toxicity (Yanai 2006). Our objective now is to understand how HTT palmitoylation regulates its other key PTMs using in vitro and in vivo models. Ultimately, we want to evaluate the therapeutic potential of modulating palmitoylation of mHTT. Here, we show new evidence of decreased palmitoylation levels in other HD mouse models. We identify new interactions between palmitoylation and key PTMs of HTT. We also demonstrate that mHTT palmitoylation can be normalized using an inhibitor of the enzymes mediating depalmitoylation (acyl protein thioesterases).

2-C-65 Stress During Gestation Augments Females' Prone to Develop Alzheimer's Disease Later in Life

Zahra Jafari[1], Bryan E. Kolb[1], Majid M. Mohajerani[1]

[1]University of Lethbridge

Alzheimer's disease (AD) consists approximately half of the dementia cases. Besides well-known risk factors for the AD, stress, and in particular noise stress (NS) is a lifestyle risk factor common today. Stress causes neurotoxic damage to cells in the hippocampus and elsewhere in the brain that may increase AD risk. Stress also has a causative association with multiple risk factors for the AD. As evidence is persistently and extensively collecting to confirm women are at significantly greater risk of developing AD than men, as well as, because maternal stress is a common adversity during pregnancy, we aimed to investigate whether gestational NS, as a common source of environmental stresses, could exacerbate development of the AD in female stressed mice than control animals. Pregnant APPNL-G-F mice were randomly assigned to either the stress condition or control group. The experimental group was exposed to the NS on gestational days 12, 14, and 16 for 24 hours. The NS paradigm caused the HPA-axis hyperactivity and increased amyloid-β (Aβ) deposition in various brain areas involved in both AD and stress regulation, especially in limbic structures; i.e., the hippocampal formation, medial prefrontal cortex, and amygdala, as well as cortical and subcortical regions. It also developed an anxiety-like behavior, deficits in learning and memory, and impaired performance in balance and motor coordination. The findings suggest the significance of protecting women against gestational stressors as a potential risk factor in accelerating AD-like neuropathological changes later in life.

2-C-66 Effects of Repeated Mild Traumatic Brain Injury on Hippocampal Synaptic Plasticity in the Juvenile Brain

Cristina Pinar[1], Christine Fontaine[1], Juan Trivino-Paredes[1], Brian Christie[1]

[1]University of Victoria

Introduction: Traumatic Brain Injury (TBI) occurs when an impulsive force is transmitted to the head and affects the brain. Up to 75% of all brain injuries are classified as "mild" TBI (mTBI; also known as concussion). There is growing evidence that, during a life time, repeated mTBI (rmTBI) can produce cumulative structural damage and long-term changes in behaviour. The juvenile brain is in a period of robust synaptic reorganization and myelination, making this a particularly vulnerable time to incur either mTBI or rmTBI. Although most children recover from mTBI incidents, a significant proportion experience learning and memory impairments after rmTBI. Memory formation is closely dependent on the capacity of the brain to regulate long-lasting changes in neuronal communication (synaptic plasticity) with the hippocampus being an essential structure for this process. Therefore, we hypothesize that rmTBI causes learning and memory deficits through its effects on hippocampal synaptic plasticity. Methods: Using the

Awake Closed-Head Injury (ACHI) model we examined how male and female rats (25-28 days of age) responded after 8 injuries over a four day period. Animals were assessed for changes in their state of consciousness and sensorimotor abilities immediately after each ACHI, allowing us to examine the acute effects of each injury. Synaptic plasticity was assessed using in vitro electrophysiology either one day or seven days post-ACHI. Results: Our results show that rmTBI impacts sensorimotor abilities and impairs hippocampal synaptic plasticity in both males and females.

2-C-67 Early seizures differentially regulate excitatory synaptic Inputs to CA1 pyramidal and interneurons in the immature brain

Ting Ting Wang[1], Hongyu Sun[1]

[1]Carleton University

The neonatal period is characterized by a critical period of synaptogenesis and plasticity, in part mediated by a physiologic imbalance between excitation and inhibition, and this imbalance is thought to contribute to the enhanced susceptibility of the immature brain to seizures and epileptogenesis. In this study, we investigated the acute effects of early life seizures on different neuronal populations in developing hippocampal CA1. Early life seizures were induced at P10-12. Double-labeling immunocytochemistry revealed that selective pyramidal neurons were activated, while no interneuron activation was detected in the immature hippocampus. Using whole cell patch-clamp recordings, CA1 interneurons and pyramidal neurons were recorded based on morphology and their distinctive electrophysiological properties. We found that intrinsic membrane properties were unchanged in both pyramidal neurons and fast-spiking PV positive interneurons from 1h post-seizure mice compared with controls. However, AMPAR-mediated sEPSCs showed significantly larger amplitude and higher frequency in pyramidal neurons from post-seizure mice compared to control neurons. Importantly, AMPAR sEPSC amplitude in both fast-spiking and non-fast-spiking interneurons from 1h post-seizure mice were not different from littermate controls, suggesting regulation of AMPAR function only occurs in selective pyramidal neurons. Our data suggest that alterations in excitatory synapses in CA1 pyramidal neurons represent a potential synaptic mechanism mediating neuronal circuit reorganization in early life epilepsy.

2-C-68 Mesoscale cortical calcium imaging reveals time-dependent functional connectivity changes in a mouse model of electroconvulsive therapy

D. Blair Jovellar[1], Jeffrey LeDue[1], Fidel Vila-Rodriguez[1], Timothy Murphy[1]

[1]University of British Columbia

Depression is a leading cause of disability worldwide. As a treatment for depression, electroconvulsive therapy (ECT) remains the most effective. Despite this, the mechanisms of ECT remain unclear. Using Electroconvulsive stimulation (ECS)--an animal model of ECT--we determine acute and chronic changes in functional connectivity after ECS. Resting state fluorescent imaging was performed in awake head-fixed mice expressing GCaMP6 (a genetically-encoded calcium indicator). GCaMP allows longitudinal imaging of intracellular Ca2+ which reflect changes in spiking activity. 10 ECS sessions were done once daily, every other day. Imaging was done daily 5-10 min and 24h post-ECS. Sham animals were handled similar to ECS animals, without electrical stimulation. Results: There are time-dependent changes in functional connectivity after ECS. Acutely, there is increased correlation of activity in sensory/motor areas and parietal association (PTA) cortex with other cortical regions. Sham animals show increased correlation of activity in retrosplenial (RS) and PTA with other cortical regions. Remarkably, 24h post-ECS, there is decreased correlation of activity in RS and PTA areas with sensory/motor regions. Sham animals maintained the increased correlation of activity in RS and PTA areas with other cortical regions seen acutely. ECS chronic effects recapitulate the decrease in functional connectivity observed in human ECT (Perrin et al., 2012) and may indicate decreased excitability due to cortical inhibition similar to what is seen in humans 24 hours after a seizure (Badawi et al, 2009).

2-C-69 CD8-expressing cell density is stage-specifically increased in chronic traumatic encephalopathy and comorbid Alzheimer's disease

Ian Mahar[1], David Kwasnik[1], Thor Stein[1], Rebecca Mathias[1], Jason Adams[1], Victor Alvarez[2], Jonathan Cherry[1], Ann McKee[1], Bertrand Huber[1]

[1]Boston University, [2]VA Boston Healthcare System

BACKGROUND The pathology for the neurodegenerative disease chronic traumatic encephalopathy (CTE) has been associated with neuroinflammation. CD8 is predominately a marker for cytotoxic T-cells that are abundant in the brain acutely following insult. CD8-expressing cells have been shown to destroy neurons in vivo. However, it is unknown whether

CD8-related neurotoxicity contributes to neurodegenerative disease, particularly for CTE. METHODS Fixed frontal cortex samples were obtained from the VA-BU-CLF Brain Bank (N=183): controls, early (stage 1-2) CTE, late (3-4) CTE, and CTE with Alzheimer's disease (CTE-AD). Sections were stained and scanned, cortical subregions traced, and staining quantified using a Leica Aperio system. ELISA values were from a Neuroinflammation Panel (Meso Scale Diagnostics). Corpus callosum thickness was measured cross-sectionally. RESULTS Late CTE and CTE-AD cases had greater sulcal CD8-expressing cell density. AT8 staining correlated with CD8 cell density, and increased between controls, early CTE, late CTE, and CTE-AD cases. Late CTE and CTE-AD cases had increased expression of ICAM1 and MDC, whereas early CTE cases showed increased IL-13. CD8-expressing cell density inversely correlated with and anterior corpus callosum thickness. CONCLUSIONS CD8 cell density is not increased in early CTE cases (despite elevated pTau), but is in later CTE stages. This may be related to increases in inflammatory cytokines in late CTE and transient IL-13 expression in early CTE. CD8 cell density is associated with white matter loss, and may contribute to symptoms.

2-C-70 Inhibiting axon degeneration

Adelaida Kolaj[1], Konstantin Feinberg[1], Chen Wu[2], Natalie Grinshtein[3], Jonathan Krieger[1], Michael Moran[1], Lee Rubin[4], Freda Miller[5], David Kaplan[1]

[1]The Hospital for Sick Children, [2]Harvard, [3]McMaster University, [4]Harvard University, [5]University of Toronto

Axon degeneration is an early event and pathological in neurodegenerative conditions and nerve injuries. To discover agents that suppress neuronal death and axonal degeneration, we performed drug screens on primary rodent neurons and identified the pan-kinase inhibitor foretinib, which potently rescued sympathetic, sensory, and motor wt and SOD1 mutant neurons from trophic factor withdrawal-induced degeneration. By using primary sympathetic neurons grown in mass cultures and Campenot chambers, we show that foretinib protected neurons by suppressing both known degenerative pathways and a new pathway involving unliganded TrkA and transcriptional regulation of the proapoptotic BH3 family members BimEL, Harakiri,and Puma, culminating in preservation of mitochondria in the degenerative setting. Foretinib delayed chemotherapy-induced and Wallerian axonal degeneration in culture by preventing axotomy-induced local energy deficit and preserving mitochondria, and peripheral Wallerian degeneration in vivo. These findings identify a new axon degeneration pathway and a potentially clinically useful therapeutic drug. We further explore the mechanism by which

unliganded TrkA transmits death signals and the summation and integration and retro- and anterograde signals at the cell body resulting in axon-selective elimination upon axon-specific injury.

2-C-71 Deletion of the GABA-A receptor's alpha1 subunit causes Juvenile Myoclonic Epilepsy (JME) and aberrant postnatal neurogenesis in mice

Sara-Ivana Calce[1], Louis-Charles Levros[2], Brianna Goldenstein[1], Ana Stoica[1], Caroline Meloche[1], Patrick Cossette[1]

[1]Centre de recherche du Centre hospitalier de l'Université de Montréal, [2]Université de Montréal

According to the literature, Gabra1-KO mice had reduced post-p19 survival and body mass. By providing additional care, we observed no differences in viability nor weight between KO and WT/HET mice. Our KO mice withstand surgical electrode implants into the cortex and hippocampus at p62 for EEG recordings. Mice recovered from surgery and were recorded each week until p97. This lead us to observe myoclonic and generalized tonic-clonic seizures in KO mice, mimicking the JME phenotype. Analysis of continuous video recordings revealed very infrequent seizures in KO mice, suggesting that brain injury (or stress) is an important environmental factor to trigger seizures in a genetically predisposed animal. Although an increasing number of causative genes in epilepsy have been identified, the mechanisms underlying epileptogenesis remain unknown. As impaired neurogenesis is associated with epilepsy, our studies reveal significant alterations in neural stem cell (NSC) homeostasis in pre or post seizure adult subventricular (SVZ) and subgranular (SGZ) zones. IHC analysis revealed that KO mice have increased proliferative (Ki67) cells in both the SVZ and SGZ, and increased numbers of neuroblasts (DCX) in the dentate gyrus, many of which were mispositioned in the hilus. Neurosphere assays showed that KOs have a significant change in NSC number in the SVZ, and in vitro differentiation assays showed that NSCs from KOs have significant cell-autonomous alterations in proliferation, neurogenesis and gliogenesis. Thus, epilepsy-associated changes in Gabra1 seem to impact neurogenesis.

2-C-72 The serine protease HtrA1 contributes to the formation of an extracellular 25-kDa apolipoprotein E fragment that stimulates neuritogenesis

Sonia Sanz Muñoz[1], Hongyun Li[1], Qian Chu[2], Alan Saghatelian[2], Lezanne Ooi[1], Brett Garner[1]

[1]University of Wollongong / IHMRI, [2]The Salk Insitute for Biological Studies

Alzheimer's disease (AD) is the most common form of dementia. The ε4 allele of the APOE gene is the major genetic risk factor for AD. Proteolytic processing of apolipoprotein E (apoE) has been identified in human post mortem brain tissue, but the enzymes responsible for apoE fragmentation are unknown, and the biological activity of specific apoE fragments remains to be determined. Here we utilised SK-N-SH neuroblastoma cells differentiated into neurons with all-trans retinoic acid (ATRA) to study extracellular apoE proteolysis. ApoE fragments were detectable in culture supernatants after 3 days, and their levels were increased for up to 9 days in the presence of ATRA. The concentration of apoE fragments was positively correlated with levels of neuronal maturation markers. We detected apoE 25 kDa and 28 kDa N-terminal fragments only in the extracellular milieu and not in cell lysates, suggesting that an extracellular protease contributes to apoE fragmentation. Of note, siRNA-mediated knockdown of high-temperature requirement serine peptidase A1 (HtrA1) and a specific HtrA1 inhibitor reduced apoE 25 kDa fragment formation by 41% and 86%, respectively. Recombinant 25-kDa fragment apoE and full-length apoE both stimulated neuritogenesis in vitro, increasing neuroblastoma neurite growth by more than 2-fold over a 6-day period. This study provides a cellular model for assessing apoE proteolysis, indicates that HtrA1 regulates apoE 25-kDa fragment formation under physiological conditions, and reveals a new neurotrophic function for the apoE 25-kDa fragment.

2-C-73 Oxytocin to mitigate the effects of prenatal alcohol exposure on neurogenesis, stress reactivity, and anxiety-like behaviour in adult male and female rats

Samantha L Baglot[1], Cecilia Fung[1], Nicole Minielly[1], Pushpkiran Ubi[1], Erin Morgan[1], Stephanie E Lieblich[1], Wayne Yu[1], Joanne Weinberg[1], Liisa AM Galea[1]

[1]University of British Columbia

Fetal alcohol spectrum disorders encompasses a range of deficits following prenatal alcohol exposure (PAE). Specifically, PAE alters the stress response and emotional regulation. The hippocampus (HPC), a brain area involved in stress and emotional regulation, shows altered neurogenesis following PAE. HPC neurogenesis may be necessary to mount an appropriate stress response. Thus, stress and emotional dysregulation following PAE may result from altered neurogenesis. Oxytocin (OT) stimulates neurogenesis and dampens the stress response in male rats. Utilizing an animal model, we examined whether OT could modulate the neurogenic, endocrine, and behavioural effects of PAE. Adult male and female offspring from PAE, pair-fed,

and control dams were treated with OT or vehicle for 10 days. We measured: corticosterone (CORT) levels before and after stress; anxiety-like and locomotor behaviour in the novelty suppressed feeding (NSF) task, and doublecortin expression in the HPC. OT caused sedative-like effects and reduced locomotion; PAE caused hyperactivity. PAE animals were faster to feed in NSF, but did not show altered approach or center time, suggesting their behaviour may reflect impulsivity. Males displayed altered CORT, and both sexes exhibited increased neurogenesis following PAE. Our data reveal novel sedative-like and locomotor changes following OT, as well as altered neurobehavioural outcomes following PAE. However, OT was not able to modulate many of the effects of PAE. Supported by NIH/NIAAA and NeuroDevNet to JW; CIHR to LAMG; and NSERC CGSM and AGF to SLB.

2-C-74 Developmental and Regenerative Roles of Arginase1 in the Nervous System

Christopher Richmond[1], Colin Funk[1], Nader Ghasemlou[1]

[1]Queen's University

Arginase1 (ARG1) is an essential urea cycle enzyme that catalyzes the hydrolysis of arginine, and is also proposed to be of importance in post-injury recovery in the nervous system (NS). Upon NS injury ARG1 is upregulated and thought to mitigate secondary damages and promote healing. In patients with genetic deficiency of ARG1, neurological phenotypes are progressive mental impairment and gait abnormalities. We therefore hypothesize that ARG1 has important neurobiological roles. In this study, we crossed Nestin-cre and loxP-flanked Arg1 mouse strains, effectively creating nestin-cre/Arg1 knockout (KO) mice, which should lack Arg1 in neural cells. Cre-loxP recombination of Arg1 was determined in a variety of tissues by PCR genotyping, confirming specificity to the NS. Further characterization of the mouse model included protein and mRNA expression analysis of various tissues to determine basal levels of Arg1. Subsequently, KO mice were compared to wild type (WT) mice for gait analysis as they aged from 2 to 6 months using DigiGait technology. To assess the role of Arg1 post-injury a sciatic nerve crush injury was used, measured by functional tests to assay differences in gait, and reinnervation of KO and WT mice. Preliminary results suggest no temporal differences in reinnervation post-injury, and gait abnormalities reminiscent of those observed in ARG1 deficient patients were absent. Our results may indicate that an absence of ARG1 in neural cells does not contribute to the phenotypes of ARG1 deficiency, nor is it likely to be important post-injury in this particular model.

2-C-75 Impaired fatty acid metabolism mediates cognitive and metabolic symptoms in Alzheimer`s disease

Laura Hamilton[1], Sandra Joppé[1], Martin Dufresne[2], Anne Aumont[1], Pierre Chaurand[3], Stephanie Fulton[4], Karl Fernandes[1]

[1]Université de Montréal, [2]Université de Montreal, [3]Univeriste de Montreal, [4]CRCHUM - Univeristé de Montréal

Alzheimer`s disease (AD), the leading cause of dementia, is classically characterized by progressive deposition of amyloid beta and hyper-phosphorylated tau. However, the numerous clinical trials targeting these inclusions have been disappointing failures. Both clinical and experimental studies indicate that many neurodegenerative disorders display coexisting metabolic dysfunctions that may cause or exacerbate the disease. In this study, we focus on this emerging line of research. We hypothesize that defects in central nervous system fatty acid signals underlie cognitive and metabolic symptoms of AD. While studying the brains of both 3xTg-AD mice and human AD patients, we observed lipid droplet accumulation along the entire rostral-caudal ventricular system and identified these lipids as triglycerides enriched with Oleic acid (OA) chains. We showed that these lipid accumulations inhibit neural stem cell proliferation and neurogenesis months prior to the onset of cognitive deficits. Moreover, central administration of a stearoyl-CoA desaturase-1(SCD-1) inhibitor, the rate-limiting enzyme in OA synthesis, decreased OA-enriched triglyceride levels, reactivated dormant neural stem cells, and prevented memory deficits in 3xTg-AD mice. Interestingly, we also found evidence of early disturbances in global energy metabolism in the 3xTg-AD model that could be rescued by central SCD-1 inhibition. Together, these studies shed light on the potential of a novel drug target SCD-1 for treatment of both the cognitive and metabolic symptoms of AD.

2-C-76 Investigating potential biomarkers of prenatal alcohol exposure using embryonic alcohol exposure in differentiating neural stem cells

Shayan Amiri[1], Carl Olson[1], Wayne Xu[1], James Davie[1], Mojgan Rastegar[1]

[1]University of Manitoba

Prenatal alcohol exposure (PAE) is able to induce a wide spectrum of mental disorders, and is considered as one of most potent environmental risks for the incidence of neurodevelopmental disorders. Recent evidence suggests that epigenetic changes of neural stem cells (NSCs) during

prenatal exposure to alcohol, mainly DNA methylation, play an important role in shaping the abnormal development of brain. In this study, we aimed to establish and validate potential biological biomarkers through genome-wide RNAseq study (Rastegar lab, in preparation for submission) by qRT-PCR, Western blot, IF and DNA dot blot assessment in an in vitro model of PAE focusing on differentiating NSCs in the forebrain of male and female embryos of C57BL/6 and CD1 strains during second trimester of pregnancy (Embryonic day 14.5). To address the sex- and strain-specific impact of PAE, our results revealed that continuous alcohol exposure altered the expression of selected developmentally important genes (identified through RNAseq) in differentiating NSCs in a strain- and sex-specific manner. Further, these changes were associated with altered DNA methylation status. We also identified and characterized the DNA methylation machinery and methylation signatures for these genes, which are relevant to brain development and clinical aspects of PAE. Investigating the epigenetic marks on altered genes is expected to help in finding potential biomarkers for early diagnosis and treatment of PAE related disorders such as fetal alcohol spectrum disorders (FASD).

2-C-77 Assessment of neurological and behavioural deficits following repeated mild traumatic brain injury in juvenile rats.

Katie Neale[1], Ryan Wortman[1], Brian Christie[1]

[1]University of Victoria

Increasing evidence shows that mild traumatic brain injury (mTBI) leads to a wide range of behavioural sequelae including cognitive, emotional and motor deficits. Children are particularly susceptible to repeated head injuries due to their high involvement in sports and risk-related behaviours. The consequences of repeat injuries, particularly at a juvenile age, are not well understood in part due to the lack of an appropriate animal model. In the current study we used a novel awake closed head injury (ACHI) model to investigate the acute behavioural consequences of repeated mTBI in male juvenile rats. Animals were administered 4 impacts (6 m/s) over a two day period. Open field, elevated plus maze, rota-rod and forced swim test performance were assessed 1 - 7 days following the last impact, and compared with performance in a SHAM group that underwent all of the experimental procedures, but did not incur any impacts. Our data indicate that the ACHI model does not produce any signs of pain in these animals, but does produce acute neurological deficits after each impact. On a longer time scale (1 - 7 days), we found that animals that experienced repeated mTBI initially show changes in anxiety-like behaviour and motor performance, but that these deficits recovered over the 7

day period. These animals did not exhibit depressive-like behaviours when tested 3-4 days after the last impact. These preliminary results indicate that the awake injury model will have significant utility for examining how repeated injuries affect brain structure and function in juvenile populations.

2-C-78 The role of PACAP-PAC1 pathway in migraine model induced by repeated electrical stimulation

Qing Zhang[1], Hangfei Wu[2], Zhao Dong[2], Weihong Song[1], Shengyuan Yu[2]

[1]University of British Columbia, [2]Chinese PLA General Hospital

Migraine is the 7th most disabling disorder globally, with prevalence of 11% worldwide. One of the prevailing mechanisms is the activation of the trigeminovascular system and calcitonin gene-related peptide (CGRP) is an important therapeutic target for migraine in this system. Recent studies suggested an emerging role of pituitary adenylate cyclase-activating peptide (PACAP) in migraine. However, the relation between CGRP and PACAP and its role in migraine remain undefined. We established a novel repeated (1, 3, 7 days) electrical stimulation (ES) model by stimulating dura mater in conscious rats. Then we determined expression patterns in trigeminal ganglion (TG) and trigeminal nucleus caudalis (TNC) of the trigeminovascular system. ES decreased facial mechanical thresholds via chronic but not acute effect, and the order of sensitivity was: vibrissa pad> inner canthus> outer canthus ($P<0.001$). ES group exhibited head-turning and head-flicks ($P<0.05$) but not resting behaviors. Importantly, ES increased the expression of CGRP, PACAP and the PACAP receptor PAC1 in both TG and TNC ($P<0.05$). However, the expression of the PACAP receptor VPAC1 and VPAC2 was increased in TG, whereas in TNC their increase was peaked on day 3 then decreased by day 7. PACAP co-localized with NeuN, PAC1, and CGRP in both TG and TNC. Our results demonstrate that repeated ES model can simulate the allodynia during the migraine chronification, and PACAP plays a role in the pathogenesis of migraine potentially via PAC1 receptor.

2-C-79 Ryanodine Receptor Type 2: a Novel Therapeutic Target for Alzheimer's Disease

Jinjing Yao[1], Bo Sun[1], Xiaoqin Zhan[1], Florian Hiess[1], Wenting Guo[1], Alexander W Chen[1], Ruiwu Wang[1], Henk Ter Keurs[1], Thomas G. Back[1], Michael Fill[2], Raymond Turner[1], S. R. Wayne Chen[1]

[1]University of Calgary, [2]Rush University Medical Center

Alzheimer's disease (AD) is the most common form of dementia with huge burden on health care globally. Unfortunately, all clinical trials on AD to date have failed, indicating that our understanding of the mechanism of AD is far from complete, and that novel and effective treatments for AD are urgently needed. Neuronal hyperactivity is an early dysfunction in AD in humans and animal models, but the mechanism underlying this hyperactivity is poorly understood. Here we define a novel mode of ryanodine receptor type-2 (RyR2) control of neuronal hyperactivity and AD progression in the 5xFAD mouse model of AD. We show that neuronal hyperactivity and memory loss in 5xFAD mice are prevented by suppressing RyR2 function. Conversely, these dysfunctions are exacerbated by enhancing RyR2 function. Interestingly, RyR2 suppression limited neuronal cell death without altering amyloid-β (Aβ) accumulation, suggesting that AD protection could be achieved despite Aβ depositions. Our data suggest that RyR2 function modulates the neuronal hyperactivity underlying AD progression, revealing RyR2 as a new (non-Aβ-directed) AD therapeutic target.

2-C-80 Obesity leads to impairment in neurogenesis and reduces brain size

Caroline Fernandes da Silva[1]

[1]Federal University of Rio de Janeiro

Overweight and obesity are public health problems that affect 30% of the world population. It is known that accumulation of body mass causes peripheral insulin resistance, diabetes, among other comorbidities. Recent studies have show that overweight also affects the nervous system, impairing cognition and increasing the propensity to develop neurodegenerative diseases, particularly Alzheimer's disease. However, the modifications in the brain as a consequence of obesity and how they affect cognition and behavior remains unclear. To investigate the impact of obesity in brain structure, we used C57/Bl6 transgenic ob/ob mice, which eats excessively due to mutations in the gene responsible for the production of leptin. Magnetic resonance imaging (MRI) was initially performed for in vivo brain volume analysis. Preliminary data show a 10% decrease in the total brain volume of the obese mice when compared to age-matched non - transgenic C57/BL6 control mice. We next carried out analysis to investigate neurogenesis, and further looked at immature neurons (using anti-doublecortin-DCX) and at the cell proliferation marker anti- Ki-67 in the brain. Both the lateral ventricle and the hippocampus were analyzed. We found important decreases in positive cells for doublecortin, as well as in cells expressing the cell cycle marker ki-67 in the lateral ventricle and in the hippocampus of ob/ob mice as

compared to controls. Our data suggests that impaired neurogenesis in the brain may contribute to cognitive deficits that obese mice develop and to the overall impact of obesity in the brain.

2-C-81 Contribution of GABAA Receptors in laterodorsal thalamic nuclei activity and Spike-Wave Discharges in WAG/Rij Rats

maryam jafarian[1]

[1]shefa neuroscience research center

Childhood Absence Epilepsy is an idiopathic generalized epilepsy. Generally, it's associated with the loss of consciousness and arrest behavior in child. This condition often improves with age. the researchers found that teens who have experienced these attacks in childhood, suffering from psychosocial problems in adulthood. Both human and experimental evidence forcefully defends the view of brain region-specific changes in phasic and tonic GABAA inhibition in typical absence seizures This study focuses on the developmental changes of GABAA receptors expression and distributions in the laterodorsal nucleus of thalamus and somatosensory cortex in animal model of absence epilepsy. Methods and Materials: Experimental groups were divided into four groups of six rats of both WAG/Rij and Wistar strains with 2 and 6 months of age. GABA expression levels of different genes that are involved in the creation of the disease, and distribution of these receptor in the somatosensory cortex and the laterodorsal nucleus of the thalamus were evaluated. Furthermore, neuronal activity changes in the laterodorsal nucleus of the thalamus and somatosensory cortex were monitored with a single unit recording and EcoG technique, simultaneously. Results: data showed gene expression levels of G-aalpha1 and G-aGama2 in the laterodorsal thalamus in four groups were not significantly different. G-aBeta3 gene expression levels in six months of WAG/Rij significantly higher than all other groups. Distribution of receptor G-aalpha1 in six months WAG / Rij was much lower than other groups. Distribution

2-C-82 Structural and functional cerebrovascular remodeling in two mouse models of ischemic stroke

Xavier Toussay[1], Cesar Comin[2], Melissa Yin[3], Luciano Da F. Costa[2], Baptiste Lacoste[4]

[1]The Ottawa Hospital Research Institute, Neuroscience Program., [2]IFSC, University of Sao Paulo, [3]FUJIFILM Visualsonics, Inc., [4]The Ottawa Hospital Research Institute, Neuroscience Program. Faculty of Medicine, University of Ott

As cerebral function relies on a steady supply of oxygen and nutrients from the blood stream (i.e. healthy blood vessels, blood-brain barrier and cerebral blood flow), the brain is particularly vulnerable to vascular failure. Aging, poor diet and other risk factors affect vascular health and promote the onset and/or progression of neurological disorders, including ischemic stroke (IS). While enhancing neuronal plasticity represents a central focus in stroke recovery, vascular responses to IS remain poorly understood. This study aims at better understanding the spatio-temporal profile of cerebrovascular responses to IS, in both female and male rodents. Our multidisciplinary approach combines anatomical and physiological methods to investigate cerebrovascular remodeling following photothrombotic or endothelin-1-mediated IS in adult outbred (Swiss Webster) mice. In the intact cerebral cortex of males, for example, we measured a vascular density of 4054±184mm/mm^3, a number of vessel branch points of 60858±5222/mm^3, and a tortuosity index of 1.32±0.05. Three weeks after IS in the peri-infarct region, both vascular density and branch points were significantly decreased (n=6; p=0.019 and p=0.004, respectively), while no difference was evidenced in tortuosity. These anatomical quantifications are complemented by sophisticated imaging modalities (photoacoustics, laser-Doppler flowmetry, PET scan) to assess functional outcomes, and will also be applied 48 hours and 1 week after IS. This work will provide a novel understanding in cerebrovascular remodeling after IS in mice.

2-C-83 Role of cerebrovascular abnormalities in the pathophysiology of autism spectrum disorders

Julie Ouellette[1], Xavier Toussay[2], Cesar Comin[3], Mirabelle Ho[4], Yen Truong[5], Cameron Morse[2], Jean-François Thibodeau[6], Melissa Yin[7], Christopher Kennedy[8], Dylan Burger[8], Luciano Da F. Costa[3], Duncan Stewart[4], Adam Shuhendler[9], Baptiste Lacoste[1]

[1]The Ottawa Hospital Research Institute, Neuroscience Program. Faculty of Medicine, University of Ott, [2]The Ottawa Hospital Research Institute, Neuroscience Program., [3]IFSC, University of Sao Paulo, [4]The Ottawa Hospital Research Institute, Regenerative Me

Brain development and function rely on vascular features that ensure proper supply of oxygen and nutrients, including the formation of vascular networks and the regulation of cerebral blood flow. Impairments in these features can lead to neurodevelopmental defects. Few studies have

considered the contribution of the brain vasculature to Autism Spectrum Disorders (ASD). Therefore, whether cerebrovascular deficits contribute to ASD pathophysiology remains unanswered. ASD are viewed as neurodevelopmental conditions associated with genetic origins. Mutations identified as possible causes for ASD include the common 16p11.2 deletion, which leads to haploinsufficiency of 26 conserved genes. We are using a multidisciplinary approach to decipher the cerebrovascular underpinnings of ASD in a mouse model of the 16p11.2 deletion syndrome. We have identified structural and functional cerebrovascular deficits during postnatal development in constitutive 16p11.2+/- mice. In particular, this model displays a significant ($p<0.01$) reduction in vascular density in the cerebral cortex at P14 (2173±37mm/mm3 in WT; 2041±23mm/mm3 in 16p11.2+/- mice), as well as a significant ($p<0.05$) increase in 16p11.2+/- mice at P50 compared to WT littermates. We also demonstrate a collection of functional abnormalities (e.g. CBF regulation) at P50 in mutant mice. In addition, we generated mice with endothelial-specific 16p11.2 deletion (Ve-Cad-Cre;16p11.2flox/+) in order to dissect the endothelial contribution to ASD phenotypes. This research program provides a novel angle to ASD research.

2-C-84 Testosterone metabolism affects hippocampal amyloid beta levels and tau phosphorylation in the 3xTg mouse model of Alzheimer's disease

Hayley Wilson[1], Ari Mendell[1], Samantha Creighton[1], Boyer Winters[1], Neil MacLusky[1]

[1]University of Guelph

Gonadal steroid hormones have been proposed to protect against the development of Alzheimer's disease (AD). The gradual decline of testosterone in aging men is associated with an increased risk for developing AD. Recent work has suggested that metabolites of testosterone that are synthesized in high concentrations in the brain may contribute to the protection provided by testosterone. In this study, we investigated whether inhibition of 5α-reductase (5α-R), the rate-liming enzyme that metabolizes testosterone into neuroactive steroids, could impact pathophysiological markers of AD in the hippocampus (HC) of male triple transgenic AD (3xTg) mice. Beginning at 6 months of age, male wild-type (WT) or 3xTg mice received daily injections of finasteride (FIN; 5α-R inhibitor; 50mg/kg i.p) or vehicle (18% β-cyclodextrin; 1% v/bw) for 20 days. Female WT and 3xTg mice received vehicle injections only. Western blots revealed hyperphosphorylation of tau in female and male 3xTg-FIN, but not vehicle control male 3xTg mice. Amyloid β (Aβ) levels were increased in all 3xTg mice, with a trend towards higher levels in the females, but minimal effect of FIN in the males. Immunohistochemical staining for Aβ was

observed in the dorsal subiculum and ventral HC. Consistent with the Western blot data, Aβ staining appeared to be stronger in the 3xTg females and 3xTg FIN males. These results suggest that 5α-reduced testosterone metabolites may contribute to the relative protection observed in males with respect to the development of AD.

2-C-85 Inhibition of 5alpha-reductase impairs object recognition memory and dysregulates hippocampal dendritic morphology in male 3xTg-AD mice

Ari Mendell[1], Samantha Creighton[1], Hayley Wilson[1], Lauren Isaacs[1], Boyer Winters[1], Neil MacLusky[1]

[1]University of Guelph

Gonadal steroid hormones protect against the development of some neurodegenerative diseases. Women are approximately twice as likely to develop Alzheimer's disease (AD) compared to men. This may be due to the drastic decline in circulating ovarian steroids that accompanies menopause, while the age-related decline in testosterone levels in men is more gradual. Recent work has suggested that 5α-reduced metabolites of testosterone may contribute to neuroprotection conferred by their parent androgen. In this study, we investigated the effects of inhibiting synthesis of neurosteroid metabolites of testosterone on object recognition memory (ORM) and hippocampal dendritic morphology in male triple transgenic AD mice (3xTg-AD). Male 6-month old wild-type (WT) or 3xTg-AD mice received daily injections of finasteride (FIN; 5α-reductase inhibitor; 50mg/kg i.p) or vehicle (18% β-cyclodextrin) for 20 days. Female WT and 3xTg-AD only received vehicle injections. Short-term ORM was significantly impaired by FIN in male 3xTg-AD, but not WT mice. Dendritic spine density (DSD) and dendritic branching of pyramidal neurons in the CA3 hippocampal subfield were reduced in 3xTg-AD females compared to WT females, while FIN decreased DSD in both WT and 3xTg-AD males. Dendritic branching was significantly reduced by FIN only in 3xTg-AD males, abolishing the observed sex difference. These results suggest that 5α-reduced neurosteroid metabolites contribute to the protection conferred by testosterone, and may play an important role in the observed sex differences in the development and severity of AD

2-C-86 Increasing APOE in primary human brain pericytes does not modify migration in a scratch-wound assay

Sonja Soo[1], Jianjia Fan[1], Wenchen Zhao[1], Jerome Robert[1], Cheryl Wellington[1]

[1]University of British Columbia

Pericytes are contractile cells that surround endothelial cells and play crucial roles in the microvasculature. Within the brain pericytes maintain the blood brain barrier (BBB) homeostasis, and lost of pericyte coverage due to migration reduces BBB integrity in Alzheimer's disease (AD). Pericytes also produce apolipoprotein E (ApoE), whose genetic isoforms confer different risks for developing AD, with apoE2 being protective and apoE4 being detrimental relative to apoE3. ApoE knockdown in murine pericytes was previously reported to promote pericyte migration, which could be rescued by exogenous apoE3 but not apoE4. As pericyte loss or migration away from the endothelial layer is thought to compromise its protective function and leaves the brain vulnerable to damage, compounds that modulate pericyte apoE expression and function may decrease pericyte migration and protect the BBB. Here we tested the hypotheses that pharmacologically increasing ApoE levels and lipidation would decrease migration of human pericytes, and that apoE genotype will influence migration. We treated primary pericytes from three donors genotyped as APOEe3/3, APOEe3/4 and APOEe4/4 with the ApoE-modulating compound GW3965. First, we confirmed that GW3965 increases the levels of secreted apoE and ATP-binding cassette transporter A1 (ABCA1), a transporter that loads lipids onto apoE. Second, we observed that GW3965 has no effect on pericyte migration in all pericyte donors, despite increased apoE, suggesting that excess apoE does not modify migration of human pericytes in a wound healing assay.

2-D-87 Robotic Quantification of Systematic Age-Related Developments in Bimanual Coordination

Stephan Dobri[1], Stephen Scott[1], T. Claire Davies[1]

[1]Queen's University

Child development stages and motor control processes are affected by neurological milestones. Quantifying the development of motor function and coordination in typically developing children can facilitate the identification of differences in pathological populations. The KINARM Exoskeleton has been used to evaluate motor impairments in adults using gamification to engage participants in tasks that test upper-limb motor function and coordination. The objective of this research was to model age-related task performance measures using KINARM tasks to assess the development of bimanual coordination in children and youths. The performance

models accounted for participant age and sex. Using these models as a basis for comparison with other neurological abilities will enable detailed understanding of neuro-motor control and enhance rehabilitation methods. A total of 206 participants (age 5-18, 142 male, 64 female) completed a bimanual coordination task. Virtual balls fell from the top of a horizontal screen and the participants were told to hit the as many balls as possible with virtual paddles. Performance was assessed using 16 different parameters which included the number of objects hit with each hand, and the total number of objects hit. The data was used to create models of age-related developments in bimanual coordination for typically developed children. A comparison with patient-specific models can provide a basis for understanding impairments in bimanual coordination related to neurological disorders.

2-D-88 The Influence of Postural Threat Type and Direction on Anticipatory Postural Control

Alyssa Bax[1], Kyle Johnson[1], Alexander Watson[1], Allan Adkin[1], Mark Carpenter[2], Craig Tokuno[1]

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

Anticipatory postural adjustments (APAs), which occur in preparation for an upcoming movement, are influenced by the context of a postural threat. To determine how the type and direction of the postural threat affect APAs, 19 young adults stood on a force plate fixed to a moveable platform and completed three blocks of trials. The first block (no threat) required participants to quickly rise onto their toes following a "go" tone. The subsequent two blocks involved the same heel raise task but were performed under threat. The threat was presented in the anterior-posterior (A-P; block 2) or medio-lateral (M-L; block 3) direction in the form of a potential unpredictable platform translation (n=10) or trunk perturbation (n=9). For each block, participants rated their anxiety. APAs were quantified by center of pressure and bilateral electromyographical (EMG) recordings of the tibialis anterior (TA). Results based on 2 (threat type: platform, trunk) x 3 (blocks: no threat, A-P threat, M-L threat) ANOVAs indicated that participants were more anxious when threatened, irrespective of threat type and direction. However, an M-L compared to an A-P threat resulted in a larger APA magnitude and velocity; this effect was consistent between trunk and platform perturbations. Further, both directions and types of threat caused similar increases in preparatory TA EMG activity. While some directional effects of postural threat on APAs were observed, other characteristics relating to postural threat may exert a stronger influence on anticipatory postural control.

2-D-89 The influence of optogenetic rebound effects on visual after-responses in mouse primary visual cortex

Jared Shapiro[1], Jillian King[1], Nathan Crowder[1]

[1]Dalhousie University

The primary visual cortex (V1) has served as a model brain region for studying cortical information processing because it is the first cortical stage of the visual pathway, and a region where several novel computations arise. A growing body of research has investigated the neural circuits underlying receptive field properties of mouse V1 neurons because the large genetic toolbox available in this species enables specific cell types to be targeted. One such genetic tool is optogenetics, which has been previously used to demonstrate the ways distinct classes of inhibitory GABAergic interneurons can balance the excitatory drive to V1 pyramidal cells. Importantly, this past work has focused on optogenetic modulation of the onset and sustained responses of V1 pyramidal neurons, but has given little attention to the pattern of activity evoked after photostimulation is terminated. Here, we use optogenetics and in vivo electrophysiological recordings to investigate the role of parvalbumin-expressing interneurons (PV+) in V1 circuitry, specifically how these interneurons affect pyramidal cell after-responses. We demonstrate that termination of optogenetic photostimulation produces a "rebound effect" on pyramidal cell activity, which facilitates after-responses. Furthermore, we distinguish whether this rebound effect occurs in a general or a specific manner.

2-D-90 Motor deterioration and Purkinje cell firing alterations in aging mice

Eviatar Fields[1], Sriram Jayabal[2], Alanna Watt[1]

[1]McGill University, [2]Stanford 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 cerebellum is critically involved in motor coordination and motor learning. Cerebellar Purkinje cells fire spontaneous action potentials at high frequencies, which is disrupted in mouse models of ataxia. Therapeutic 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. It has been hypothesized that neurodegenerative

diseases like ataxia share common mechanisms with aging, 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 mechanistic underpinnings.

2-D-91 Effects of Magnocellular Selective Inhibition on Dorsal Stream Vision-For-Action Tasks.

Megan McFadyen[1], Jenni Karl[1]

[1]Thompson Rivers University

Milner and Goodale's action-perception theory proposes that the dorsal stream enables vision-for-action, like reaching out to grasp an object, whereas the ventral stream enables vision-for-perception, such as recognizing that object. There is evidence that magnocellular (M) and parvocellular (P) pathways map on to the dorsal and ventral streams but there is no behavioural evidence that the M pathway selectively enables vision-for-action and the P pathway vision-for-perception. We hypothesized that if the action-perception theory extends to the M and P pathways then selective inhibition of the M pathway should impair dorsal stream vision-for-action tasks, but not ventral stream vision-for-perception tasks. Participants performed a grasping (vision-for-action) task by reaching out to grasp a target embedded within an ebbinghaus illusion. They also performed an estimating (vision-for-perception) task by simply opening their index finger and thumb to match the perceived size of that same target. These tasks were performed in a white light condition and a red light condition as diffuse red light is known to selectively inhibit the M pathway. Maximum opening of the index finger and thumb was recorded during both tasks using electromagnetic sensors attached to the participants' fingers. It was expected that the accuracy of index-thumb opening would be impaired on the grasping, but not estimating task in the red light condition. The results are discussed in relation to whether or not this supports the proposition to extend the action-perception theory to the M and P pathways.

2-D-92 Single neuron defined cortico-subcortical mesoscale networks are associated with specific motor actions in awake chronic mice.

Dongsheng Xiao[1], Jeffrey LeDue[1], Matthieu Vanni[1], Timothy Murphy[1]

[1]University of British Columbia

How information processing in motor pathways drives a specific action is still largely unknown. Difficulty comes from recording neural activity over large spatial scales while monitoring motor output and single neuron responses. We provide a chronic recording system which integrates with wide-field calcium functional imaging, multi-site sub-cortical cellular electrophysiology and peripheral nerve recording in head-fixed mice which undergo self-initiated bouts of running and or facial movements. Facial motor nerve impulses were measured by paired fine wire recording. Mesoscale GCaMP imaging was used to assess regional cortical activity. Nerve or single neuron spike-triggered averaging allowed the identification of cortical regions that are preferentially related to specific actions. Multiple tetrodes were then implanted in regions of interest to record extracellular spike activity. Spontaneous firing of facial motor neurons is linked to specific patterns of cortical mesoscopic activity, and unexpectedly was found to be associated with unique patterns of cortical activation which extended to higher-order associative cortical areas, including RS, PTA, ACC and mPFC. Preliminary results also indicated cortico-hippocampal networks associated with rhythmic nose movement and a cortico-VTA network was associated with spontaneous running. We suggest that these large scale brain networks coordinate spontaneous running and whisking associated movements. Our findings are consistent with specific behavioral actions involving large scale brain networks.

2-D-93 Therapeutic exercise in a mouse model of spinocerebellar ataxia type 6

Anna Cook[1], Sriram Jayabal[2], Mohini Bhade[1], Alanna Watt[1]

[1]McGill University, [2]Stanford University

Spinocerebellar ataxia type 6 (SCA6) is a late-onset polyglutamine expansion disease whereby an extended CAG sequence in the CACNA1A calcium channel gene causes symptoms of ataxia and eventual cerebellar degeneration. Treatment options are limited and the pathophysiology is incompletely understood. We used a knock in mouse model with a pathogenic variant of the CACNA1A gene containing an expanded CAG repeat (84Q) to investigate the pathophysiology of the disease. We have shown that at 7 months these mice display significant deficits in firing

precision and frequency of Purkinje cells. Previously, we identified the drug 4-Aminopyrimidine (4-AP) as a potential treatment, with chronic oral administration leading to a partial rescue of SCA6 pathology and complete rescue of Purkinje cell firing precision, with no change in frequency (Jayabal et al., 2016). We wondered whether other treatment avenues could rescue motor deficits in our SCA684Q/84Q mice. Exercise has been shown to have neuroprotective effects in humans and improves motor coordination in several mouse models of ataxias. We investigated whether exercise affected our SCA684Q/84Q mouse model using a program of voluntary exercise and observed a partial rescue of motor behaviour and Purkinje cell abnormalities. In contrast to 4-AP, we found that exercise improved Purkinje cell firing frequency without affecting firing precision. Our results suggest that both Purkinje cell rate and precision deficits contribute to SCA6 pathology, and thus a combination therapy approach may be optimal to improve motor coordination in SCA6.

2-D-94 Shape-mask similarity seems to influence successful localization of a masked target shape

Robert Whitwell[1], James Enns[1], Robert Foley[2]

[1]The University of British Columbia, [2]Carleton University

In an effort to overcome some of the problems associated with subjective report as a criterion for conscious awareness, we have developed an alternative criterion based on 'flexible and intentional use of information'. In the present study, participants performed a shape localization task in which one of four possible pre-cued target shapes was presented briefly among two distractor shapes. On each trial, the three shapes were rendered less visible by four-dot object-substitution masks that persisted on view after the brief display had terminated. We varied the target shape and the trial schedule for the target shape (blocked separately vs. randomized), the target eccentricity, and the mode of responding. So far, we have tested eye movements and classic button-press mode of responding, and our next steps include testing other modes of responding and inverting the task instruction to localize a non-target. Our preliminary results across two studies reveal a remarkably powerful effect of target shape, such that participants are far more sensitive to localizing square targets among diamond distractors than they are diamond targets among square distractors. Furthermore, participants are least sensitive to localizing leftward pointing triangles amongst rightward pointing ones or vice versa. These preliminary findings suggest that the square implied by the four-dot mask boosts the visibility of a target square, in comparison to a target diamond or triangle.

2-D-95 Optogenetic Modulation of GABAergic Interneurons Affects Contrast Response Functions in Mouse Primary Visual Cortex

Jillian King[1], Cheryl Gill[1], Rachel Erskine[1], Jared Shapiro[1], Nathan Crowder[1]

[1]Dalhousie University

The visual system has long been used to study cortical information processing. Recent work in the mouse has taken advantage of several genetic tools to examine the roles of specific cell types in shaping the response properties of neurons in the primary visual cortex (V1). Studies using optogenetic modulation of parvalbumin (Pvb+) and somatostatin (Sst+) expressing GABAergic interneurons indicate that these two populations may counteract the excitatory activity of pyramidal neurons (Pyr) in different ways. However, this past work has produced contradictory findings on whether these cell types act in either a subtractive or divisive manner. Here we combined single unit electrophysiology with optogenetic modulation of either Pvb+ or Sst+ interneurons to provide additional data to help resolve some of these contradictory findings. We used a variety of photo-stimulation intensities and focused on V1 neurons' response to spatial contrast, which had not been emphasized in past work. We then fit neural responses obtained during photo-stimulation to models of subtractive or divisive inhibition to objectively compare our findings to past work.

2-D-96 Distinct Neural Signatures of Reward and Sensory Prediction Error in Motor Learning

Dimitrios Palidis[1], Joshua Cashaback[1], Paul Gribble[1]

[1]University of Western Ontario

Adaptation of motor output to changing environments occurs by multiple distinct processes. In sensory error based learning, it is thought that the nervous system predicts the low level sensory consequences of motor commands, and that sensory prediction error drives learning when sensory input violates these predictions. In reinforcement learning, it is thought that the brain predicts the subjective value of actions, and that reward prediction error drives learning when the outcome value differs from that which is expected. Actions that produce better than expected outcomes are reinforced while actions that produce worse than expected outcomes

are deterred. We recorded EEG from humans of either sex to identify and dissociate the neural correlates of reward prediction error and sensory prediction error during two different learning tasks designed to isolate each response. We observed sensory error based learning in a visuomotor rotation task, in which learning occurred in response to altered visuospatial feedback of hand position. In a reward learning task, learning occurred in response to binary reward feedback. We found that a fronto-central event related potential called the feedback related negativity occurred specifically in response to reward prediction error during reward based learning, while a more posterior component called the P300 was associated with SPE during a visuomotor rotation task. These findings reveal a dissociation between well characterized EEG signatures of error processing in two distinct motor learning processes.

2-D-97 Altered sensory processing during absence seizures: a view from inside cortical and thalamic neurons.

Mark Williams[1], Sarah Lecas[1], Severine Mahon[1], Stéphane Charpier[1]

[1]ICM - Brain and Spine Institute

Epileptic seizures ensue from deviant cellular and/or synaptic properties and may lead to an altered processing of ongoing information by neurons. During absence seizures, spike-and-wave discharges (SWDs) interfere with incoming sensory inputs, participating in the looseness of conscious experience. However, the mechanisms by which SWDs alter conscious perception remain unclear. Using the Genetic Absence Epilepsy Rat from Strasbourg (GAERS), a validated animal model of absence epilepsy, we identified cellular correlates leading to conflicting interactions between epileptic discharges and sensory processing. By combining in vivo electrocorticographic and intracellular recordings from the somatosensory cortex of GAERS, we found that the intrinsic excitability of cortical neurons was dynamically altered during seizures, alternating periods of increased and decreased cell responsiveness. To investigate how this time-dependent change in cortical excitability affected sensory processing during absence seizures, we now examined at single cell level the whisker-evoked sensory responses in the related thalamo-cortical system in the course of SWDs. Sensory stimuli were still processed in the neurons of primary sensory cortices and thalamic nuclei during SWDs but with a severe time-to-time variability depending on the Spike or Wave component in the EEG. This lack of consistent sensory responses in the somatosensory thalamo-cortical network and neurons could, at least partly, explain the interruption of conscious perception during absence seizures.

2-D-98 Continuous modulation of human spinal cord function in advance of thermal pain assessed with fMRI

Patrick Stroman[1], Patrick Stroman[1], Gabriela Ioachim[1]

[1]Queen's University

Our prior studies of descending pain regulation using functional magnetic resonance imaging (fMRI) in the human brainstem (BS) and cervical spinal cord (SC) have identified both reactive and continuous responses when participants were prompted to anticipate a noxious stimulus. In order to further investigate the continuous component of descending regulation we analyzed data from 56 healthy female participants in prior studies using similar predictable pain stimulation paradigms. We hypothesized that systematic BOLD signal variations occur throughout fMRI studies involving a predictable noxious stimulus, even prior to the application of the stimulus. FMRI data were pre-processed to correct for motion, remove physiological noise, and were spatially normalized. Data were analyzed by means of Bayesian regression to a model approximating the dependence of BOLD responses on pain ratings and stimulus temperature. We also applied dynamic structural equation modeling (SEM) to the data for each participant, and connectivity strengths between regions at different times during the stimulation paradigm were analyzed in relation to individual pain ratings. The results confirmed our hypothesis and support the conclusion that homeostatic autonomic control influences the receptive state that modulates pain responses. This control appears to occur via the hypothalamus, PBN, and NTS, to influence the PAG-RVM-SC descending pain modulation pathway. The results identify properties of pain processing in the healthy human brainstem and spinal cord, and mechanisms for variation across individuals.

2-D-99 Dissecting Neural Circuits Underlying Delayed Motor Learning of 16p11.2+/- Mice

Xuming Yin[1], Nabil Asraoui[1], Marie-Eve Mathieu[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. Despite the common prevalence of this disorder, there are clinical studies that report ASD patients also exhibit motor deficits and clumsiness. However, the neuronal pathophysiology underlying these symptoms remains elusive. We

developed a novel motor task on a head-fixed running wheel apparatus, and found that the 16p11.2+/- mice did not show any movement deficits but exhibited delayed motor learning compared to wild-type mice. Interestingly, we identified a region- and layer-specific loss of noradrenergic (NA) innervation in the L2/3 of the primary motor cortex of 16p11.2+/- mice, which was also accompanied by a deficit in c-fos labelled neurons after motor training. To examine whether there are structural abnormalities in L2/3 pyramid neurons of 16p11.2+/- mice during learning, we employed in vivo two-photon imaging to chronically monitor spine dynamics in awake and behaving mice. We found that 16p11.2+/- mice have a significantly higher density of dendritic spines compared to wild-type mice. However, despite this baseline spine density aberrance, our preliminary data shows that 16p11.2+/- mice have the same learning-induced spine formation as wild-type mice, but have a slower process of spine pruning. These results suggest that deletion of the 16p11.2 locus results in a layer- and region- specific loss of NA innervations that is accompanied with deficits in synaptic reorganization, ensemble activation, and delayed motor learning.

2-E-100 Conductance-based model of subfornical organ neurons predicts integration of cardiovascular and inflammatory signals

Laura Medlock[1], Nick Simpson[1], Dominic Standage[1], Alastair Ferguson[1]

[1]Queen's University

The subfornical organ (SFO), a sensory circumventricular organ, has been implicated in a wide range of autonomic nervous system (ANS) function, including cardiovascular and immune homeostasis. Emerging evidence suggests that the SFO may be integrating pro-inflammatory and fluid balance signals to potentiate angiotensin II (ANG II)-induced hypertension at the SFO. However, the neuronal mechanisms underlying this signal integration have yet to be investigated due to the limitations of single technique approaches to experimental design. To overcome these limitations, we combined in vitro electrophysiology and our previously established mathematical model of SFO neurons to study the integration of tumor necrosis factor-α (TNFα), a pro-inflammatory cytokine, and ANG II, a peptide hormone traditionally known for its pressor effects. Our model predicts that 24hr incubation in TNFα, demonstrated by a shift in the transient Na+ activation curve, will potentiate an SFO neurons response to ANG II. These findings are supported by preliminary results from in vitro patch-clamp recordings of dissociated SFO neurons. Analysis of membrane dynamics characterized the neuronal

mechanisms supporting this signal integration. Future use of this model will allow us to study the integration of various ANS signals within the SFO.

2-E-101 Fluoxetine increased IL-1beta in the maternal hippocampus and reversed maternal care deficits with postpartum corticosterone treatment but not depressive-like behaviour

Wansu Qiu[1], Kim Go[1], Rand Mahmoud[1], Natasha Black[1], Aarthi Gobinath[1], Paula Duarte-Guterman[1], Liisa Galea[1]

[1]University of British Columbia

Postpartum depression affects approximately up to 10-15% of women. Fluoxetine is a common selective serotonin re-uptake inhibitor (SSRI) prescribed to treat postpartum depression. The pleiotropic cytokine interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) are elevated in patients with depression compared to healthy controls. Here, we used a rodent model of postpartum depression to determine how maternal stress hormone exposure and SSRI treatment affect the cytokine levels within the maternal brain. We hypothesized that maternal corticosterone and SSRI treatment will have a more inflammatory cytokine profile than non-treated control dams. Dams were given corticosterone (40mg/kg) to model postpartum depression and fluoxetine (10mg/kg) for 21 days. Dams were tested for depressive-like behaviour using the Forced-swim test (FST) at the end of their treatment period. Then dams were sacrificed and brain tissues were used for cytokine analysis. Preliminary cytokine data showed a decrease in IL-6 and TNF-α within the hippocampus in corticosterone treated dams. Fluoxetine treatment increased the levels of interleukin-1beta (IL-1β) within the dam hippocampus. Further analyses will look at the cytokine profile within the prefrontal cortex of the dams to determine any possible effects by brain region. With more understanding of how antidepressant and maternal stress hormone exposure can affect the cytokine signatures within the brain, it can provide insights as to whether pregnant women or new mothers will seek antidepressants or alternative treatments for depression.

2-E-102 Aromatase expression in the neocortex of adult male rats

Chloe Soutar[1], Patrick Grenier[1], Mary Olmstead[1], Hans Dringenberg[1]

[1]Queen's University

The steroid hormone estradiol (E2) rapidly influences synaptic activity and plasticity in the rodent forebrain. Aromatase, the enzyme responsible for the terminal step of E2 biosynthesis, has been detected in the sensory neocortex of mice and primates. Previous work in our lab has demonstrated that local application of an aromatase inhibitor within the primary auditory cortex (A1) of adult male rats reduces long-term potentiation, suggesting that E2 is synthesized in A1 and acts as a local modulator of long-term synaptic plasticity. Surprisingly, it appears that no prior work has examined aromatase expression in the rat neocortex. Thus, we examined the expression pattern of aromatase in the sensory neocortex of adult male rats. Using 3,3'-diaminobenzedine immunohistochemistry (IHC), we found that aromatase is widely expressed in the rat A1. Aromatase immunoreactivity increased linearly across cortical layers I to VI and did not differ significantly between hemispheres. These results indicate that the rat A1 is a site of E2 synthesis and provide the first description of aromatase expression within the rat neocortex. Preliminary data show a similar level of aromatase immunoreactivity in the primary visual cortex of male rats. Ongoing experiments are centered on investigating the expression pattern of aromatase in other neocortical regions (e.g., primary somatosensory cortex) and the cellular localization of aromatase using fluorescent IHC to detect co-localization of neocortical aromatase with markers for neurons, glia, and glutamatergic cells (supported by NSERC and CIHR).

2-E-103 Expression and release of growth hormone from the B lymphocytes of the chicken bursa of Fabricius: Action of hypothalamic hormones

Santiago Pech Pool[1], Laura Berumen[1], Carlos Martínez Moreno[2], Guadalupe García Alcocer[1], Martha Carranza Salas[2], Carlos Arámburo[3], Maricela Luna Muñoz[3]

[1]Autonomous University of Querétaro, [2]National Autonomous University of México, [3]Instituto de Neurobiología, UNAM Campus Juriquilla

Growth hormone (GH) is expressed in immune cells in which exerts immunomodulatory effects. However, the mechanisms of expression and release of GH in the immune system remains unclear. Since the classical regulatory hormones (Growth hormone releasing hormone [GHRH], Thyrotropin releasing hormone [TRH], ghrelin and somatostatin [SST]) and their receptors are expressed in B cells, we analyzed the effect of these peptides in B-bursal cells (BBCs). The mRNA expression and GH release as well as the changes upon the CREB phosphorylation and calcium mobilization were determined after the treatments with these hormones. The presence of the

receptors of TRH, ghrelin and SST were confirmed; however, the GHRH-R was absent in the BBCs (by RT-PCR and immunohistochemistry). The GH mRNA was increased by TRH and decreased by SST (RT-qPCR). The mobilization of intracellular calcium was increased only by SST (colorimetric assay). Only TRH increased the phosphorylation of CREB (SDS-PAGE-WB). Finally, TRH and SST decreased the release of GH to the culture media (SDS-PAGE-WB). Contrary to expectation, GHRH and ghrelin did not have effect on B-cell GH expression and release. Our findings suggest a differential regulation of the immune GH expression compared that of the pituitary GH, since in BBCs apparently TRH and SST are the main regulators. We acknowledge the technical support of: Courtois G., González A., Hernández N. Financtial support: PAPIIT-DGAPA-UNAM 200717, 201817, 207018, CONACYT: 421484. Thanks to Pilgrims México for the donation of chicken embryos.

2-E-104 Perinatal Exposure to a Contaminant Mixture: Effects on Estrogen Receptor Expression in the Ventral Tegmental Area

Sandra Konji[1], Hannah Landry[1], Dana Tabet[1], Anne TM Konkle[1]

[1]University of Ottawa

Introduction: Maternal behaviour is a collection of behaviours by the mother that can increase offspring survival. Estrogens bind and activate estrogen receptors in various brain areas, including the Ventral Tegmental Area (VTA). The continuance of maternal behaviour is tied to the action of neurotransmitter receptors in this region. Gestational exposure to an environmental contaminant mixture, composed of organochlorine pesticides, polychlorinated biphenyls (PCB) and methylmercury, has been shown to impact offspring behaviours at various ages. However, no studies have explored any neurotoxic effects of this exposure on the maternal brain. Our work aims to characterize the effects of exposure to this toxicant mixture on the number of estrogen receptors in the VTA as this could impact maternal behaviour. Methods: Female rats were dosed during pregnancy and until weaning with the full mixture (4.00mg/kg/day or 0.04mg/kg/day), MeHg (1.0mg/kg/day or 0.01mg/kg/day) or corn oil vehicle; n=22 total. Immunohistochemistry for estrogen receptor alpha was performed on 30 µm fixed brain sections. Immunopositive cells were counted with Image J. Results: Results of an ANOVA reveal no effect of treatment on ER alpha counts in the VTA of day 21 postpartum dams. Conclusions/Significance: While some changes in the postpartum brain are transient, our data indicate that any potential early postpartum ER alpha changes do not persist in the VTA.

2-E-105 Stress-induced Activation of Discrete Projection Neuron Populations in the Basolateral Amygdala

Robert Aukema[1], Andrei Nastase[1], Matthew Hill[1]

[1]University of Calgary

The basolateral amygdala (BLA) is an important brain region activated by psychological stress, acting to integrate sensory information with higher-order cognitive input. In turn, it projects to several brain regions capable of modulating various behavioral and physiological processes. However, it is unclear which projection populations are recruited during stress exposure and how each population individually contributes to the overall stress response. Thus, in a rat model, we investigated BLA projection populations recruited by exposure to acute stress by using a combination of anatomical tracing (to label discrete projections) and c-fos mapping (to identify neural activity). We first characterized projection targets of BLA neurons by injecting AAV8-CaMKII-eGFP into the BLA and analyzing GFP fiber density throughout the brain. Consistent with classical anatomical studies, fibers from BLA neurons were seen in many stress regulatory brain regions. We next examined which projection neurons were activated by restraint stress. As expected, 30 minutes of restraint increased c-fos expression throughout the BLA. Discrete BLA projection populations were identified by choleratoxin subunit B and examined for colocalization with c-fos following stress exposure. Preliminary data indicates that stress increased c-fos in projection neurons targeting the prelimbic cortex, ventral hippocampus, and nucleus accumbens. This suggests that these projections are important in the collective stress response, and provides a framework to now begin investigating the individual role of each projection.

2-E-106 Formaldehyde Induces Diabetes-related Cognitive Dysfunction

Yun Zhang[1], Tan Tao[2], Wenhong Luo[3], Jihui Lv[4], Chanshuai Han[5], Jason N.R. Hamlin[5], Hongjun Luo[3], Hui Li[3], You Wan[6], Yang Xu[7], Zhiqian Tong[2], Weihong Song[8]

[1]The University of British Columbia, [2]Capital Medical University, [3]Shantou University Medical College, [4]Beijing Geriatric Hospital, [5]McGill University, [6]Peking University, [7]Central China Normal University, [8]University of British Columbia

Patients suffering from type 2 diabetes mellitus (T2DM) often experience a significant decline in cognitive function. Hyperglycaemia is one of the most prominent characteristics of diabetes, but

how glycemic state contributes to cognitive dysfunction in T2DM remains elusive. Mitochondrial aldehyde dehydrogenase (ALDH2) is the major enzyme responsible for oxidizing FA and is ubiquitously expressed to promptly metabolize excess FA. Here, we report that T2DM patients with mutation in ALDH2 gene had higher levels of FA associated with more severe dementia. Ablation of ALDH2 gene expression induced abnormally high levels of FA, leading to hyperglycaemia and cognitive impairments in mice. In addition, we found that excess FA interacts with insulin and impairs insulin signalling pathway, which contributes to memory decline in diabetic rodents. Reduction of FA by transgenic overexpression of hALDH2 attenuates hyperglycaemia and alleviates cognitive deficits in different diabetic mouse models. These findings indicate the deleterious role of excess FA in mediating diabetic-related dementia. Targeting FA and its metabolizing enzyme ALDH2 may be a promising approach for preventing and treating dementia in diabetics.

2-E-107 Genetic deletion of melanin-concentrating hormone receptor 1 from GABAergic neurons in the nucleus accumbens increases ambulatory activity

Alex Hebert[1], Stephen Flaherty III[2], Nadege Briançon[2], Pavlos Pissios[2], Jeffrey Flier[3], Eleftheria Maratos-Flier[2], Melissa Chee[1]

[1]Carleton University, [2]Beth Israel Deaconess Medical Center, Harvard Medical School, [3]Harvard Medical School

Melanin-concentrating hormone (MCH) plays a key role in regulating energy balance. In rodents, MCH acts via the receptor MCHR1, and MCHR1 deletion increases both energy expenditure and ambulatory activity. While MCHR1 expression is widespread, most MCHR1 neurons are GABAergic in nature. To determine the role of these neurons in MCH-mediated energy balance, we conditionally deleted MCHR1 from neurons expressing the vesicular GABA transporter (vGAT). To accomplish this, we generated an MCHR1-flox mouse and then crossed it with a vGAT-cre mouse. The resulting vGAT-MCHR1-KO (cKO) mice had decreased body weights, increased energy expenditure, and pronounced hyperactivity relative to vGAT-cre controls. In order to identify the critical GABAergic MCHR1 neurons that mediate this effect on ambulation, we injected a virus encoding cre recombinase into specific regions of the MCHR1-flox brain. Deleting MCHR1 from the nucleus accumbens (NAcc) increased ambulatory activity by 82%. Dopamine has been implicated in the effects of MCH on ambulation, and we found that blocking dopamine reuptake with GBR12909 increased the hyperactivity of cKO mice twice as much as controls. Furthermore, GBR12909 application during in vitro amperometry recordings

from striatal slices revealed enhanced dopamine release in the NAcc of cKO mice. Consistent with this, amperometry recordings showed that MCH application suppresses dopamine release by 24% in the NAcc of control but not cKO mice. These results suggest that MCH regulates energy balance via GABAergic NAcc neurons in part by inhibiting dopamine release.

2-F-108 SLC6A3 Polymorphism Affects Ability to Encode, but not Recall, Abstract Images in Medicated Parkinson?s Disease

Brian Robertson[1], Abdullah Al Jaja[2], Ken Seergobin[3], Nole Hiebert[2], Adrian Owen[2], Penny MacDonald[4]

[1]Schulich School of Medicine and Dentistry / Western University, [2]Brain and Mind Institute/ Western University, [3]University of Western Ontario, [4]Western University

Cognitive dysfunction occurs in Parkinson's Disease (PD). At baseline, cognitive functions mediated by the dorsal striatum (DS), an area that receives inputs from the substantia nigra pars compacta, are impaired. Cognitive functions mediated by brain regions receiving dopamine from the relatively-spared ventral tegmental area (VTA) are intact, and actually worsen with dopamine supplementation. Dopamine transporter (DAT), encoded by gene SLC6A3, is a transporter that resorbs dopamine. In the SLC6A3 gene, a 40-base-pair variable repeat element exists, with 9- (9R) and 10-repeat (10R) forms. Presence of the SLC6A3 9R allele causes higher DAT levels (and lower baseline synaptic dopamine concentrations) than 10R-homozygosity. We investigated the effect of SLC6A3 polymorphisms on response to dopaminergic therapy of cognitive functions mediated by VTA-innervated brain regions (i.e., encoding abstract images) versus DS (i.e., recall abstract images). We found that dopaminergic therapy worsened encoding of abstract images in 9R-carriers only. In contrast, dopaminergic therapy improved recall of abstract images in all PD patients irrespective of SLC6A3 genotype. We found that 9R-carrier status predisposes to dopamine overdose and impairment of cognitive functions mediated by VTA-innervated brain regions. This genetic background does not modulate improvement of DS function related to dopaminergic therapy in PD. Understanding how SLC6A3 polymorphisms affect cognition and response to dopaminergic therapy in PD could lead to more personalized treatment regimens.

2-F-109 Cognitive, emotional, and postural adaptations to repeated postural threat exposure

Kyle Johnson[1], Martin Zaback[2], Craig Tokuno[1], Mark Carpenter[2], Allan Adkin[1]

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

Postural threat influences emotional, cognitive and postural responses. As limited work has explored individuals' capacity to adapt threat-related responses, we examined the effects of repeated threat exposure on anxiety, attention, and postural measures in young (N=28) and older (N=14) adults. Participants stood on a force plate fixed to a translating platform. Threat was changed by altering the expectation of receiving an unpredictable left- or rightward platform perturbation. A 60-s stance trial was completed with no perturbation threat (NT) followed by 24 trials with perturbation threat. For 6 threat trials, participants stood for 60-s prior to being perturbed (T1-6). A NT trial was also completed after the threat trials (NT2). Participants rated their anxiety and attention to different information. Centre of pressure (COP) and skin conductance response frequency were calculated. 2(age group) x 2(threat; NT, T1) and 2(age group) x4(threat; T2, T4, T6, NT2) ANOVAs examined initial threat and threat exposure effects, respectively. With threat, both groups were more anxious and physiologically aroused, reported broad attention changes, and increased COP amplitude and frequency. Emotional and cognitive responses adapted to repeated threat exposure but COP responses did not, except for high frequency sway (which decreased in young but increased in older adults). Results suggest emotional and cognitive responses adapt to repeated threat exposure but do not return to no threat levels. Sway frequency changes suggest age influences postural adaptation to threat. NSERC funded.

2-F-110 The influence of lactate dehydrogenase on long-term memory in Drosophila melanogaster

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

[1]Western University

Over the last decade glial cells have emerged as key regulators of memory. One way glial cells influence memory is by aiding in brain metabolism. Studies in vertebrate models such as mice, rats and chicken have revealed that astrocyte derived lactate promotes long-term memory (LTM). Specifically, astrocytes convert pyruvate to lactate during the last step in glycolysis using the enzyme lactate dehydrogenase and this metabolite is subsequently shuttled to neurons for

fuelling oxidative metabolism. Alterations in this neuro-metabolic coupling may underlie age-related memory impairment observed in most animals; a theory that has yet to be formally tested. The recent finding that glial glycolysis in the brain of fruit flies (Drosophila melanogaster) provides a source of lactate to ensure neuronal survival indicates that invertebrate brain glia may function similarly to the astrocyte-neuron lactate shuttle present in vertebrates. The objective in this study was to determine whether lactate metabolism in flies can influence LTM formation. Drosophila lactate dehydrogenase (ImpL3) expression was altered in glial cells. Memory was assessed using courtship-conditioning, whereby the ability of male flies to remember exposure to unreceptive females 24 hours prior is a measure of LTM. Preliminary results suggest that elevated ImpL3 expression is detrimental to the health of flies and reducing ImpL3 may increase lifespan. These preliminary findings suggest that elevated lactate production may actually be detrimental to central nervous system function, particularly with age.

2-F-111 Developing novel mouse lines to investigate the roles of TAN-secreted ACh and Glu

Ornela Kljakic[1], Helena Janickova[1], Mohammed Al Onaizi[1], Salah Mestikawy[2], Marco Prado[1], Vania Prado[1]

[1]Robarts Research Institute, University of Western Ontario, [2]McGill University

Cholinergic tonically active neurons (TANs) co-express vesicular acetylcholine transporter (VAT) and vesicular glutamate transporter 3 (VG3) and thus can store and release acetylcholine (ACh) and glutamate (Glu). Recent studies suggest that the balance between ACh and Glu is critical for controlling striatal-dependent behaviour. We hypothesize that TAN-secreted ACh and Glu differentially regulate striatal function, where a balance favouring ACh may facilitate cognition processing and a balance favouring Glu may control reward behaviour. We selectively eliminated VAT or VG3 in VG3-positive cells that expressed an excitatory Dreadd (VG3CreDrd) to generate mice with an altered striatal balance of ACh and Glu (VG3CreVATFxDrd, VG3CreVG3FxDrd). This allowed us to selectively stimulate TANs to release ACh or Glu thereby discerning their striatal roles. Characterization indicated VG3Cre is ectopic and therefore Drd expression is not selective to TANs. Nonetheless, initial CNO tests did confirm the excitatory Drd was functional as all three Drd-expressing mouse lines exhibited a clear hypoactive phenotype. Furthermore, in the absence of Drd expression CNO did not interfere with behaviour. To selectively target TANs, we bilaterally implanted cannulas in the dorsal striatum of our mouse models. Ultimately, we developed novel chemogenetic mouse lines in order to investigate the roles of TAN-secreted

ACh and Glu in striatal associated behaviours. These mouse lines will now be used to determine if activation of TANs by local CNO infusion can interfere with striatal associated functions.

2-F-112 Motor learning and execution: Involvement of Akt3-GSK-3 pathway

Bruno Ouimet[1], Michel Cyr[1]

[1]Université du Québec à Trois-Rivières

In humans and animals, learning a skilled motor task requires integration of many signals from different parts of the brain especially the basal ganglia, motor cortex, and cerebellum. It is well known that once learned, a motor skilled task is performed automatically and never totally forgotten. However, the underlying molecular mechanisms of this learning process are not well-understood. Akt is a highly conserved kinase among mammals and regulates several metabolisms such as proliferation, survival and neuronal plasticity. Akt has three isoforms and it is important to note that Akt3 isoform is significantly more expressed in the brain than its other two isoforms. Akt and GSK-3 are intimately connected. It is well established that Akt reduces the activity of GSK-3 by its phosphorylation on specific site. In the present study, using genetic and pharmacological tools, we investigated whether Akt3 and GSK-3 play a role in motor learning and abilities. In order to study a skilled motor task in mice, we used the accelerating rotarod, which is well known to reproduce learning phases. The results obtained demonstrated that Akt3 deletion compromised rotarod performances. Interestingly, our results demonstrated a change of the phosphorylation of GSK-3 and propose that the motor training deficit would be caused by GSK-3 hyperactivation, induced by the genetic deletion of Akt3. It is interesting to note that lithium chronic treatment, re-established the training deficit of Akt3 KO mice. Our results have established an important implication of the Akt3/GSK -3 pathway in motor training.

2-F-113 High-throughput touchscreen tasks and open access database integration to accelerate drug discovery for neurodegenerative disorders

Flavio Beraldo[1], Daniel Palmer[1], David Wasserman[1], Benjamin Kolisnyk[2], Samantha Creighton[3], Justin Mels[1], Wai-Jane Lee[1], Matthew Cowan[1], Chris Fodor[1], Tom Gee[4], Robert Bartha[1], Stephen Strother[4], Tim Bussey[5], Lisa Saksida[1], Vania Prado[6], Boyer Winters[3], M

[1]University of Western Ontario, [2]Rockefeller University, [3]University of Guelph, [4]Rotman Research Institute, [5]Western University, [6]Robarts Research Institute, University of Western Ontario

Bussey-Saksida touchscreen tasks provide innovative ways to assess cognition in rodents for basic research and drug discovery because of their similarity to human tests, automation and potential for high-throughput. We evaluated the performance of three mouse models of Alzheimer's disease (AD) (5XFAD, 3xTG-AD and APP/PS1) to address the hypothesis that they have common cognitive deficits that can be unmasked by touchscreen tasks. Male and female mice were tested longitudinally on the 5-Choice Serial Reaction Time Task (5-CSRTT-attention), Pairwise Discrimination with reversal (PVD-cognitive flexibility) and Paired Associate Learning (PAL-learning and memory). All data were verified using a newly developed automated quality control procedure and then entered into a large-scale open-access searchable database. Behaviour was highly reproducible between two sites at Western and Guelph. We detected attention deficits in both the 3xTG-AD and the 5xFAD mouse lines. None of the mouse lines presented deficits in PVD, but all three strains displayed deficits in PAL. This methodology can be applied to other mouse models of neurodegenerative disease(Parkinson's and Amyotrophic Lateral Sclerosis/FTD). Our approach will expand the repertoire of touchscreen tests matched to specific mouse models of neurodegeneration and make the results publicly available in order to highlight the potential of these behavioural assays for drug screening. This integrated approach could accelerate drug discovery for a variety of neurodegenerative diseases by defining and sharing robust cognitive endpoints.

2-F-114 Aerobic glycolysis is required for spatial memory consolidation but not memory retrieval in mice

Richard Harris[1], Asad Lone[2], Heeseung Lim[2], Timothy Scholl[2], Robert Cumming[3]

[1]University of Ottawa, [2]University of Western Ontario, [3]Western University

Aerobic glycolysis (AG), the non-oxidative metabolism of glucose to generate lactate even when oxygen is not rate limiting, is believed to be critical for long-term memory formation. We previously demonstrated that lactate dehydrogenase A (Ldha) and pyruvate dehydrogenase kinase 1 (Pdk1), key enzymes which promote AG, exhibit an age-dependent decline in the frontal cortex of wild type mice. Moreover, improved memory performance in aged wild type mice correlates with elevated expression of both Pdk1 and Ldha. In this study we tested the effect of dichloroacetate (DCA), an inhibitor of Pdk1, on spatial memory in mice using the Morris Water Maze. In vivo hyperpolarized 13C-pyruvate magnetic resonance spectroscopy revealed

that DCA administration leads to the decreased conversion of pyruvate to lactate in the mouse brain, concomitant with a reduction in phosphorylation of the PDH complex. Intraperitoneal (IP) injection of DCA during each training session caused a significant delay in learning which subsequently resulted in impaired spatial memory assessed by both short-term and long-term probe trials. Surprisingly, a single IP injection of DCA before the probe trials had no effect on memory performance. Our findings indicate that AG plays a key role during memory acquisition and consolidation but is less important for retrieval of established memories. Thus, regional activation of AG may be critical for learning-dependent synaptic plasticity rather than the activation of signalling cascades required for retrieval or reconsolidation of established spatial memories.

2-F-115 Glutamatergic modulation of dopamine activity in the nucleus accumbens can enhance or inhibit motivation as a function of recent failure or success

David Lindenbach[1], Anthony Phillips[1], Jeremy Seamans[1]

[1]University of British Columbia

Dopamine signalling in the nucleus accumbens is critical for determining how much effort will be expended towards achieving a desired outcome. The ventral subiculum sends a glutamate projection to the nucleus accumbens, positively regulating dopamine release. Through modulation of dopamine tone, we hypothesized that the ventral subiculum should regulate the amount of effort that an organism will expend to earn food rewards under increasingly demanding conditions. In rats, selective modulation of the ventral subiculum to nucleus accumbens glutamate pathway was achieved with optogenetics, using a virus coding for channelrhodopsin (for neural activation), halorhodopsin (for neural inhibition) or a fluorescent protein (as a control). Animals were food-restricted and trained on a progressive-ratio (PR) lever-pressing task using sugar pellets as the reward, with the break-point defined as the final ratio successfully achieved. Light was used to modulate neural activity 1) prior to beginning a session 2) after successfully completing a PR near an animal's normal break-point or 3) after failing to complete a PR. Halorhodopsin-mediated inhibition reduced the speed and frequency of lever pressing only when given after successfully completing a PR near the break-point. Channelrhodopsin-mediated activation increased the speed and frequency of lever pressing only when given after failing to complete a PR. By demonstrating that the ventral subiculum to nucleus accumbens glutamate pathway bidirectionally controls motivation, we highlight a novel therapeutic target to treat anhedonia.

2-F-116 The role of microbiota in major depressive disorder: a pilot study in gnotobiotic mice.

Marc Louis-Auguste[1], Giada De Palma[1], Jun Lu[1], Elena Verdu[1], Rebecca Anglin[1], Mike Surette[1], Steve Collins[1], Premysl Bercik[1]

[1]Farncombe Institute, McMaster University

Background: The etiology of major depressive disorder (MDD) is poorly understood. Current evidence suggests immune activation and gut microbiota may play a role. Recent studies suggest that behavioural traits can be transferred through microbiota transplantation into germ-free (GF) mice. Here we study whether microbiota from patients with MDD can induce depressive-like behavior. Methods: GF NIH Swiss mice were colonized with stool microbiota from a patient with MDD with elevated fecal β-defensin 2, or a healthy donor (HV). After three weeks, behavior was assessed using standard tests. Expression of neuroimmune markers was assessed in the gut and brain using gene expression profiling and immunohistochemistry. Microbiota composition was assessed by 16S rRNA sequencing. Results: Microbiota profiles differed between the two groups of mice (p=0.001). Mice with MDD microbiota exhibited lower preference for sucrose (p=0.002) and more emotionality (p=0.003) than mice with HV microbiota. This was associated with lower BDNF expression in the caudate putamen (p=0.02), and a similar trend in the frontal cortex (p=0.054). MDD mice had altered expression of multiple genes, including those encoding for colonic occludin (p=0.01), jejunal GABAB receptor (p= 0.02) and chemokine receptor CXCR3 (p=0.03). In summary, GF mice colonized with MDD microbiota exhibit depression-like behaviors. This appears to be accompanied by changes in intestinal permeability and neuroimmune function. These results suggest that gut microbiota has the capacity to influence the expression of MDD in some patients.

2-F-117 Independent effects of age and levodopa on reversal learning in healthy volunteers

Andrew Vo[1], Ken Seergobin[1], Penny MacDonald[2]

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

The dopamine overdose hypothesis has provided an important theoretical framework for understanding cognition in Parkinson's disease. It posits that effects of dopaminergic therapy on cognition in Parkinson's disease depend on baseline dopamine levels in brain regions that support different functions. Whereas functions performed by more severely dopamine-depleted brain regions improve with medication, those associated with less dopamine deficient areas are actually worsened. It is presumed that medication-related worsening of cognition owes to dopamine overdose. We investigated whether age-related changes in baseline dopamine levels would modulate effects of dopaminergic therapy on reward-learning in healthy volunteers. In a double-blind, crossover design, healthy younger and older adults completed a probabilistic reversal learning task following treatment with 100/25 mg of levodopa/carbidopa versus placebo. Older adults learned more poorly than younger adults at baseline, being more likely to shift responses following misleading punishment. Levodopa worsened stimulus-reward learning relative to placebo to the same extent in both groups, irrespective of differences in baseline performance and expected dopamine levels. When Order effects were eliminated, levodopa induced response shifts following reward more often than placebo. Our results reveal independent deleterious effects of age group and exogenous dopamine on reward learning, suggesting a more complex scenario than predicted by the dopamine overdose hypothesis.

2-F-118 Adaptation and retention of standing balance changes following prolonged exposure to height-related threat

Martin Zaback[1], Minh Luu[1], Allan Adkin[2], Mark Carpenter[1]

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

Recent work examining the effect of repeated threat exposure suggests that some threat-related changes in standing balance are adopted regardless of one's emotional response to threat. This study used blocked repeated exposure to height-related postural threat to determine if changes in standing balance persist after the emotional response to threat is abolished. Six young adults stood on a force plate fixed to the edge of a hydraulic lift for 2-min standing trials performed at LOW (0.8m above ground; away from edge) and HIGH threat (3.2m above ground; at edge). HIGH threat trials were repeated 15 times to examine adaptation. Subjects returned after 4-8 weeks to repeat standing trials at LOW and HIGH threat to examine retention of adapted behaviours. Self-reported confidence, fear, anxiety and attention focus were recorded as well as centre of pressure (COP) and electrodermal activity. Initial changes with threat involved reduced confidence, increased fear, anxiety, and arousal, and broad attentional changes; balance

changed with increased COP frequency, decreased COP amplitude, and leaning of the mean position away from the edge. After blocked exposure, all cognitive and emotional outcomes returned to LOW values along with COP frequency; however, changes in COP amplitude and leaning persisted. On the 2nd visit, cognitive and emotional responses to threat partially re-emerged, but COP frequency remained equal to LOW. These preliminary results confirm that some threat-related changes in standing balance are adopted irrespective of one's emotional response to threat.

2-F-119 Microglial GPR120 plays an essential role in the prevention of inflammation

Geneviève Demers[1], Jérôme Roy[1], Diane Bairamian[1], Khalil Bouyakdan[1], Nathalie Arbour[1], Cyril Laurent[1], Vincent Poitout[1], Guillaume Ferreira[2], Stephanie Fulton[3], Thierry Alquier[1]

[1]Centre de recherche du CHUM, [2]Institut national de la recherche agronomique (INRA), [3]CRCHUM - Univeristé de Montréal

Objective: GPR120 is a receptor for polyunsaturated fatty acids and omega-3s. Peripherally, GPR120 is highly expressed in macrophages and is implicated in the resolution of inflammation. In this context, obesity has been shown to exacerbate neuroinflammation, which aggravates anxio-depressive-like behaviors. In this study our objectives were to: (1) determine the cellular expression pattern of GPR120 in the brain (2) investigate its anti-inflammatory action in primary microglia cells and (3) determine if a GPR120 agonist (cpdA) exerts protective effects on neuroinflammation and sickness behavior induced by lipopolysaccharide (LPS). Methods: GPR120 expression was assessed in multiple mouse brain regions and in primary mouse and human microglia, astrocytes and neurons. CpdA was applied to mouse primary microglia cultures before LPS to measure the pro-inflammatory response. CpdA (10 µg) was administered ICV for 3 days in C57Bl/6 male mice followed by an intraperitoneal injection (IP) of LPS (0.83 mg/kg) or saline. Behavioral tests were performed subsequently. Results and conclusions: GPR120 is mainly expressed in microglia. CpdA decreases LPS-induced expression and secretion of pro-inflammatory cytokines in microglia cultures. The beneficial effects of cpdA are absent in GPR120-deficient microglial cells. In vivo, ICV cpdA strongly decreases neuroinflammation in the nucleus accumbens and LPS-induced sickness behavior. In conclusion, GPR120 activation prevents LPS-induced microglial activation, inflammation and sickness behavior.

2-F-120 A novel platform for quantifying social interactions: mesocopic dual brain imaging of GCaMP mice

Federico Bolanos[1], Luis Bolanos[1], Jeffrey LeDue[1], Matilde Balbi[1], Matthieu Vanni[1], Dongsheng Xiao[1], Allen Chan[1], Timothy Murphy[1]

[1]University of British Columbia

The power of social interaction and touch is undisputed across the animal kingdom. To evaluate neuro-correlates of social behaviour, recent studies have focused both on system level human studies to mechanistic studies within animal models. In animals, studies have largely focused on social interactions between rodents, and this work indicates a fundamental role of the rodent vibrissa system in transmitting social signals. While considerable work has been done in both human and animal models, there have been no evaluated correlations between subjects over high sampling rates and relatively large expanses of the cortex. Here, we employ mouse mesoscale GCaMP imaging to establish how brain functional networks cooperate in simultaneously imaged GCaMP6s mice. The setup begins with the mice 110mm away from each other for 1.5 minutes, then one of the setups is moved towards the other setup at a constant speed of ~9mm/s until the snouts of the mice are 5mm apart. At this distance the mice are able to interact with their whiskers. Then at the 4 minute mark the mice are separated back to the initial state. We observe no inter-mouse correlations when the mice are separated but when the mice are within interaction distance the posterior part of the barrel cortex and the parietal temporal association areas between the mice are highly correlated. Upon closer inspection of the behaviour and imaging data, the high correlations correspond to large calcium transients evoked by mutual whisking between the mice.

2-F-122 Internal states of low self-efficacy can induce learned nocebo effects on thermal sensation in youth

Ella Weik[1], Christine Tipper[2], Regula Neuenschwander[1], Karin Jensen[3], Tim Oberlander[2]

[1]University of British Columbia, BC Childrens Research Institute, [2]University of British Columbia, [3]Karolinska Institute

This study investigates if internal states can influence thermal sensation after an associative learning paradigm in youth. We hypothesize that statements that engage an internal sense of high and low self-efficacy (SE) can induce learned placebo and nocebo responses to thermal stimulation. N = 26 youth described an autobiographical memory related to a high, low and

neutral SE statement, completed a thermal perception paradigm, the Adult Hope Scale and the State-Trait-Anxiety-Inventory. During a thermal perception paradigm participants were asked to recall the memory associated with the presented SE statement. In a conditioning phase the high SE/low SE statement was paired with an individually calibrated low/high thermal intensity. During the testing phase, the low, high and neutral SE statements were presented with a moderate thermal stimulus. Participants rated their discomfort from 0-100. Moderate thermal stimuli were rated as more uncomfortable when paired with a conditioned low SE state compared to the conditioned high SE and neutral SE state (nocebo effect). There was no difference between high SE and neutral SE state (placebo effect). The magnitude of the nocebo effect was positively correlated with trait anxiety and negatively with hope. Conditioning of thermal sensations with internal self efficacy states result in significant nocebo effects, but no placebo effects. Personality factors such as hope and anxiety influence the magnitude of the nocebo effect. This study contributes to identifying the underlying mechanism of nocebo responses in youth.

2-F-123 Age, rather than body weight, is a determinant of cognitive abilities in certain inbred mouse strains

Gabor Nagy[1], Gyorgy Levay[1]

[1]Gedeon Richter Plc

The successful development of procognitive drugs is heavily dependent on the availability of valid animal models that show cognitive impairment. A major concern of such models has always been their translatability. Today, a wide variety of genetic engineering methods allow the rapid construction of genetically modified strains where specific loci underlie cognitive malfunction. However, a general concern with these models is their high specificity; the fact that they each harbor a mutation(s) that usually is found only in a very small fraction of human patients with impaired cognition. Therefore, there is still a need for animal models that are clearly less specific and allow for the testing of procognitive drug candidates. Based on previous findings, we sought to test the usability of high-fat diets on eliciting chronic cognitive decline in C57BL/6J mice and in a BXD RI strain, both known inbred strains. Simple learning and memory tests such as the novel place recognition and spontaneous alternation were performed before and after keeping animals for four months on a high-fat or normal diet. To our surprise - and contrary to the findings of others - we found that body weight gain is not a good predictor of cognitive decline, neither across different inbred strains, nor across individuals of a given strain.

We conclude that certain inbred strains that average high on learning and memory tests at a young age rather than strains that are prone to obesity may be used for modeling progressive decline. Supported by Richter Plc and by NAP 1.0 Grant from the Hungarian Government.

2-F-124 Ablation of hippocampal neurogenesis and chronic inhibition of immature hippocampal neurons with DREADDs differently affect delay-based decision-making

Desiree Seib[1], Delane Espinueva[1], Oren Princz-Lebel[1], Erin Chahley[1], Stan Floresco[1], Jason Snyder[1]

[1]University of British Columbia

There is evidence that reduced adult hippocampal neurogenesis plays an important role in depression. Assigning less value to future rewards is a hippocampus dependent trait of depression. We want to elucidate if manipulations of neurogenesis can affect valuation of delayed rewards. Thus, we combine novel rat models in which we either block neurogenesis (GFAP-TK) or inhibit new neurons using the DREADD system and complex behavioural operant testing paradigms. We first tested TK rats on a delay discounting paradigm, where animals must choose between a low immediate reward and a larger delayed reward. Compared to WT rats, TK rats showed a decreased preference for the high reward with increasing delay times, indicating that neurogenesis increases the subjective value of future rewards. We were able to replicate this by ablating neurogenesis with irradiation in WT rats. On the contrary, increasing neurogenesis by running led to increased preference for the delayed high reward. Second, we inactivated hM4D(Gi) expressing immature neurons with chronic CNO injections. Interestingly, chronically silencing immature neurons resulted in an increased preference for the delayed reward. This project uses novel rat models to study the impact of neurogenesis on future thinking. It suggests that increased neurogenesis through exercise could benefit depressed patients. Importantly, this study shows that different methods of inhibiting neurogenesis or silencing new neurons can result in different behavioural phenotypes and we yet have to identify the mechanism why and how these manifest.

2-F-125 Within-session intermittent cocaine self-administration produces addiction-like behaviours in rats, even with short daily sessions

Florence Allain[1], Anne-Noël Samaha[2]

[1]UdeM, [2]Université de Montréal

To model cocaine addiction, rats typically self-administer cocaine continuously during daily extended 6-h sessions (Long Access, LgA). Compared to shorter sessions (1-2h), LgA-sessions evoke greater drug intake and promote patterns of drug use relevant to addiction. This has led to the belief that taking large amounts of drug continuously is necessary to develop an addiction phenotype. However, cocaine addicts might take the drug intermittently rather than continuously within a bout of intoxication (Beveridge et al., 2012). The intermittent access (IntA) self-administration procedure models this in rats, whereby cocaine is available in 5-min drug periods intercalated with 25-min no-drug periods (Zimmer et al., 2011). While IntA-rats self-administer less cocaine than LgA-rats, they show greater incentive motivation for cocaine (Zimmer et al., 2012), and only three IntA-sessions can sensitize incentive motivation for cocaine (Calipari et al., 2015). IntA-sessions are also long, typically lasting 6h. Here, we determined whether IntA-sessions must be extended to evoke addiction symptoms. Two groups of male rats self-administered cocaine for 18 daily IntA-sessions. Rats had access to either 6-h or 2-h sessions. IntA-6h rats self-administered more cocaine than IntA-2h rats but both developed robust psychomotor sensitization and a binge-like pattern of drug use. Both groups also showed similar levels of incentive motivation for cocaine and cocaine-induced reinstatement of drug seeking behavior. Thus, even short daily IntA-sessions can promote the development of addiction symptoms.

2-F-126 Variability in Cognitive Trajectories: Validation Study of the Kaplan-Baycrest Neurocognitive Assessment (KBNA)

Natalia Ladyka-Wojcik[1], Kristoffer Romero[1], Larry Leach[1], Guy Proulx[1]

[1]Glendon College of York University

The variability within and between optimal aging, normal ageing and dementia populations highlights the need for sensitive neuropsychological assessments for studying them. One such assessment tool is the Kaplan-Baycrest Neurocognitive Assessment (KBNA). Based on previous research and validation studies of the KBNA, it is possible to dissociate specific dementias including Alzheimer's disease and vascular dementia. However, the exact sensitivity of the KBNA still needs to be clarified in order to strengthen its clinical utility. This study reviews which subtests of this assessment can isolate mixed dementias (e.g. Alzheimer's disease with vascular symptoms), as well as identify normal ageing and optimal aging populations. It also seeks to give better understanding of the factors that underlie the variability in cognitive performance in

these distinct populations. Through a retrospective chart review (N=300), a multivariate analysis (partial least squares) was used to evaluate these questions. Results demonstrated that the KBNA is sufficiently sensitive for optimal and normal ageing populations, and identified specific subtests in working and episodic memory that can consistently identify patients with symptoms of mixed Alxheimer's-vascular dementia. Overall, this study contributes to the current understanding of underlying cognitive profiles of each group, with implications in effective clinical assessment of cognitive functioning in dementia and normal ageing.

2-F-127 Enhancing the inhibition control associated with the left prefrontal cortex by increasing connectivity in the right prefrontal cortex: a tDCS-fMRI study

Abrar Alhindi[1], Natalie Wright[1], Eun Hyung Choi[1], Lawrence Ryner[1], Andrew Goertzen[1], Colleen Millikin[1], Ji Hyun Ko[1]

[1]University of Manitoba

Introduction: Prior fMRI studies have suggested that the left superior frontal gyrus (SFG) is associated with inhibition control, the ability to control attention to override strong internal urges or external distraction. The lateralization of resting-state functional connectivity in relation to inhibition control has not been validated. Method: 23 healthy subjects (8 males; age 47.1±14.3; MoCA≥26) were assessed with resting-state fMRI and Stroop task, before and after transcranial direct current stimulation (tDCS; 15 minutes; 1.5mA). The anode was placed on left (n=7) or right SFG (n=7). The rest (n=9) received sham tDCS. The degree centrality (DC; a measurement of functional connectivity) of the left and right SFG was estimated based on graph theory analysis. Results: At baseline, Stroop interference score (the degree of successful inhibition) was correlated with the left SFG DC ($r=0.678$, $p<0.001$) but not with the right SFG ($r=0.278$, $p=0.199$). The right SFG stimulation increased the right SFG DC ($t(6)=2.877$, $p=0.028$) which was associated with a trend level of increased interference score ($t(6)=2.352$, $p=0.057$). Sham or left SFG stimulation did not induce significant changes in either DC or Stroop interference ($p>0.10$). Discussion: Our results suggest that individuals with higher left SFG connectivity at baseline have better inhibition control over the word interference. Increasing the functional connectivity of the right SFG by anode tDCS further enhanced inhibition performance, potentially suggesting a complementary role of the right hemisphere in the Stroop task.

2-F-128 Are teacher ratings of self-regulation more accurate than parent ratings in children with acquired brain injuries?

Stela Musteata[1], Chand Taneja[2], Esther Direnfeld[3], Mauricio Garcia-Barrera[1]

[1]University of Victoria, [2]Island Health Authority/University of Victoria, [3]Hamilton Health Sciences

Parent and Teacher rating scales (PRS, TRS) are commonly used by researchers and clinicians to aid the assessment of self-regulation problems. However, third-party ratings may measure different aspects of self-regulation, from what is assessed on standardized performance-based tasks. This study examined if measures of self-regulation on a computerized neurocognitive assessment, CNS Vital Signs (CNSvs), were correlated to the Behavior Assessment System for Children, Second Edition (BASC-2) Executive Functioning (EF) scale and components in children with acquired brain injuries from a community clinic. Of 224 paediatric cases available, 26 (MAge=13.66, SDAge=2.71, range 9-18) completed both instruments. First, the relationship between BASC-2 EF (PRS, TRS) and CNSvs EF domain was examined, and, no relation was found. In post-hoc analyses, we correlated BASC-EF components (Attention Problems: AP and Hyperactivity: H) to CNSvs self-regulation components (e.g., Complex Attention: CA and Psychomotor Speed: PS). A highly significant correlation was observed between BASC-2 AP TRS and CNSvs CA (r= -.464; p= .00). No significant correlation was observed between BASC-2 AP PRS and performance on the CNSvs CA. Neither parent nor teacher ratings of Hyperactivity were related to observed test performance. These results emphasized the importance of teacher?s observations of self-regulation post-injury, though further investigations are required.

2-F-129 A Comparison of 2-Dimensional and 3-Dimensional Multiple Object Tracking Training

Erika Shaw[1], Brian Christie[1]

[1]University of Victoria

The NeuroTracker (NT), a computerized 3-Dimensional Multiple Object Tracking (3D-MOT) training device; has potential benefits for injury reduction, concussion management and reduction of fatigue-related mistakes. Accessing 3D technology is a limiting factor for 3D-MOT, so we assessed the performance of MOT training in both 2D and 3D environments. Nineteen participants completed ten training sessions over a three-month period and were assigned to one of four groups: 2D only, 3D only, 2D switching to 3D, and 3D switching to 2D. On the first and final training session the 3rd edition of the Sport Concussion Assessment Test, the King

Devick, and a ruler reaction time assessment were used as control tests to examine cognitive status. In all groups performance increased with training, indicating individuals could learn in all conditions. However, groups that maintained training in either the 2D or 3D environment showed a 60% improvement in performance on average, whereas individuals in the two groups that switched environments only averaged a 32% increase in NT performance. Individuals training in 3D only achieved the greatest performance increase (70%) overall. These results suggest that 2D and 3D MOT are different tasks, and that switching between the two environments can be detrimental to learning performance. Because interpreting 2D cues involves different cognitive faculties than normal 3D perception, clarification of whether a 2D environment engages higher levels of attention, and memory, or a 3D environment produces higher visual processing speeds is required.

2-F-130 Sex differences in the role of adult neurogenesis in visuo-spatial learning and memory is dependent on stress during training.

Timothy O'Leary[1], Delane Espinueva[1], Desiree Seib[1], Jason Snyder[1]

[1]University of British Columbia

Adult hippocampal neurogenesis in rodents is involved in visuo-spatial learning and memory, and regulation of the hypothamic-pituitary-adrenal axis and stress-related behaviour. It is not clear, however, how the role of adult-born neurons in learning and memory is influenced by stress during the learning episode. We used the GFAP-TK transgenic rat that expresses the herpes simplex virus thymidine kinase under the glial fibrillary acidic protein promoter, to reduce adult neurogenesis with the drug valganciclovir. Both male and female GFAP-TK and wild-type Long-Evans rats were tested in the Morris water maze using either cold 16°C (high stress) or warm 25°C water (low to moderate stress). Rats completed 3 days (4 trials/day) of acquisition training followed by a probe trial (60 sec) to assess memory. In 16°C water, male WT rats showed better learning performance than GFAP-TK rats, whereas female rats showed the opposite result, because GFAP-TK rats showed better learning performance than WT rats. These differences between genotypes were not found in 25°C water. In the probe trial, there was a trend for better memory performance in male WT than GFAP-TK rats in 16°C water. Overall, sex differences were found at 25°C but not 16°C, where male rats showed superior learning and memory. These results suggest that in both sexes, adult neurogenesis is involved to in visuo-spatial learning and memory to a larger degree during stressful learning episodes. While

learning and memory performance of males is impaired when neurogenesis is ablation, performance of females is enhanced.

2-F-131 Age-related bidirectional regulation of object memory by the lysine acetyltransferase PCAF 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

Histone acetylation, catalyzed by lysine acetyltransferases (KATs), plays a critical role in the transcriptional regulation that supports mnemonic processes. Dysregulated histone acetylation in Alzheimer's disease (AD) is associated with repression of learning and memory genes and expression of apoptotic genes. There is growing evidence that restoring histone acetylation, by increasing KAT activity, has therapeutic potential. Interestingly, the KAT, PCAF, may function atypically in AD. While PCAF activation enhances memory in normal rodents, in Aß-treated rats, PCAF inhibition or KO attenuates AD-like cognitive deficits, suggesting PCAF activity may 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 using the object location task. Our findings reveal a unique and complex role for PCAF in the progression of AD that has implications for therapeutic strategies.

2-F-132 Roles of the basolateral and central nuclei of the amygdala in reward-related behaviors: Studies using in vivo optogenetics

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

[1]*Université de Montréal*

The amygdala is thought to attribute predictive and reinforcing values to reward-paired cues. We hypothesized that optogenetic stimulation of neurons in the basolateral (BLA) or the central (CeA) nuclei promotes the predictive and reinforcing values of a reward cue. First, we determined whether optogenetic stimulation of these neurons alone was reinforcing. If so, it could confound interpretation of eventual effects on the response to reward cues. Rats received bilateral injections of a virus delivering ChR2 or a control virus in the BLA or CeA to transfect neurons selectively. Optic fibers were also implanted for subsequent photostimulation. Using in vivo electrophysiology, we first found that photostimulation (473 nm, 10 mW, 5-ms pulses at 5-20 Hz) increased BLA and CeA neuron firing only in the presence of ChR2. In a second cohort, we allowed rats to press a lever to earn photostimulations in the BLA or CeA, paired with a light-tone cue. Relative to controls, CeA but not BLA rats pressed more on the active lever and earned more photostimulations, across fixed, random and progressive ratio schedules of reinforcement. Laser frequency influenced lever-pressing behaviour (20 Hz > 5 Hz). When active and inactive levers were reversed, CeA rats showed reversal learning and pressed more on the new active lever. Thus, optogenetic activation of CeA, but not BLA neurons is reinforcing. We are now determining whether optogenetic stimulation of BLA neurons influences the response to reward cues. The results will provide new knowledge on the role of the amygdala in reward function.

2-F-133 Can meditation strategies improve attention in older adults with a history of falls?

Sabrina Ford[1], Lindsay Nagamatsu[1]

[1]*Western University*

Falls in older adults are a major health care concern given the resulting injuries and medical costs. Previous literature suggests that recurrent falls among older adults are not merely accidents, but rather caused by intrinsic factors. One such factor that has been linked to falls is poor attention. A strategy that has been shown to improve attention in other populations is meditation. Meditation can be defined as regulation of the self and bringing awareness and focus to the present moment. Therefore, our current study examined whether using meditation training in an older adult population with a history of recurrent falls would improve their attention. We conducted a four-week intervention where participants were randomly assigned to either a: 1) focused meditation condition, or 2) an acoustic music listening (control) condition three times a week. Before and after the four-week intervention we assessed attention using: 1)

the Sustained Attention to Response Task (SART) which measured reaction time and accuracy, and 2) EEG during resting state where we measured alpha peak frequency (iAPF). Our results show a significant improvement in SART performance and increase in iAPF in the meditation group compared to the control group. These results suggest that focused attention meditation can increase attention in older adults, possibly decreasing their risk of falls and reducing falls-related injuries. In conclusion, the use of focused attention meditation in older adults may provide an accessible intervention to improve mobility, and therefore independence and quality of life.

2-F-134 Working Memory and Falls Risk in Older Adults

Yee (Michelle) Wong[1], Lindsay Nagamatsu[1]

[1]Western University

BACKGROUND: The aging population is rapidly increasing, where currently the population of older adults (ages 60) outnumbers the population of children. Falls risk is major concern for older adults, as falls can impair instrumental activities of daily living. Thus, understanding the factors that attribute to falls risk is vital. Cognition function, specifically global cognition and executive function have shown to be impaired in fallers. However, working memory has not been examined as a falls risk factor. PURPOSE: To examine if there is a relationship between mobility and working memory in older community-dwelling adults. METHODS: Older adults (n=38, female=23) aged 60-80 years (m=69.56, SD=4.74) completed two sessions. The first session incorporated a battery of cognitive and mobility tests. Participants were placed into a low-risk (LR) or a moderate risk (MR) group based on their mobility test results and/or their falls history. The second session had participants engage in 3 versions (0, 1, 2) of the n-back test. Electroencephalograms (EEG) and behavioural performance were recorded. RESULTS: Results indicated that 5x Chair Stand and Trail Making Test (B-A) ($p<0.05$) were significantly associated with increased falls risk. In the 2-back test, the MR group had a longer response time, were less accurate, and exhibited alterations in the N300 ERP component. CONCLUSIONS: Falls risk is associated with poorer performance on higher order working memory tasks. From our results, future studies should consider investigating the mechanisms between working memory and falls risk.

2-F-135 Mind Over Matter: Understanding the Relationship Between Memory Self-Efficacy, Cognition and Brain Health in Older Adults with Probable Mild Cognitive Impairment; A Pilot Study

Rebecca Horst[1], Lindsay Nagamatsu[1]

[1]Western University

In our aging population, cognitive decline and brain health are critical areas of concern for healthy aging. Evidence has shown that personality factors such as self-efficacy, one's personal perceived ability to perform a specific task, directly impacts components of healthy aging. However, it is unknown whether memory self-efficacy (MSE), specifically, might be associated with aspects of brain health; namely functional activity and structure. We hypothesize that memory self-efficacy will be independently associated with functional activity and structural volumes in regions of interest pertaining to memory. Using a cross-sectional design, community dwelling older women with probable Mild Cognitive Impairment (MCI) were asked to evaluate their memory self-efficacy using the Memory Self-Efficacy Questionnaire (MSEQ-4) and the Multifactorial Memory Questionnaire (MMQ) in addition to standardized cognitive tests. Using a 3T SIEMENS scanner, T1 weighted structural imaging and BOLD signal fMRI, during an associative-memory task, was obtained. Multivariate linear regression models were constructed for brain health measures in relation to MSE measures, co-varying for age and physical activity level. Our models found that the MMQ subscale Feelings of Contentment (MMQ-F) was the strongest measure in accounting for variance in mean % signal change and structural volumes of the hippocampi and white matter. Based on the results collected it appears that one's perceived self-efficacy of memory feeling and contentment is associated with measures of cognition and brain health.

2-F-136 Assessing cognitive function and brain health in older adults at-risk for diabetes

Joyla Furlano[1], Lindsay Nagamatsu[1]

[1]Western University

Older adults with type 2 diabetes (T2D) experience cognitive decline and cerebral atrophy, and therefore are at high risk for developing dementia. Consequently, older adults at-risk for developing T2D (based on high body mass and blood glucose levels) are at higher risk for cognitive decline. Pre-diabetic older adults have been shown to experience some cognitive decline, however 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 currently unknown in this population. Therefore, the aim of this study was to assess cognitive performance and brain health in older adults at-risk for T2D. We conducted a cross-sectional analysis of older adults (aged 60-80) at-risk for T2D (BMI > 25 or blood glucose of 6.1-7.0 mmol/L) and healthy aged-matched controls, examining 1) executive functioning and memory performance using a battery of neuropsychological tests, 2) functional brain activation, as measured by fMRI, and 3) structural measures such as volume of the hippocampus. Based on our cross-sectional analysis, older adults at-risk for T2D show impaired executive functioning and memory performance, as well as altered brain structure and function that may contribute to the observed deficits. We conclude that older adults at-risk for T2D experience cognitive decline and decreased brain health, and future studies should examine lifestyle intervention strategies to prevent or delay the onset of such decline.

2-F-137 Association Between Cognitive Reserve and Cognitive Performance in People with HIV: A Systematic Review and Meta-Analysis

Navaldeep Kaur[1], Nandini Dendukuri[1], Lesley Fellows[1], Marie-Josée Brouillette[1], Nancy Mayo[1]

[1]McGill University

Background: Cognitive reserve is a potential explanation for the disparity between brain pathology and its clinical manifestations. Milder forms of HIV-associated neurologic disorders predominate despite revolutionized treatments. Although cognitive reserve has been studied in relation to cognitive ability in HIV, a quantitative synthesis has not been undertaken. Objectives: The main objective was to estimate, based on published studies, the strength of the association between cognitive reserve and cognitive performance in individuals with HIV. Methods: A systematic literature search using Ovid MEDLINE, PsychINFO, and EMBASE was performed to identify studies published between 1990 -2016 that quantified the association between cognitive reserve and cognitive performance in HIV. A random-effects meta-analysis was used to compute a summary estimate with 95% confidence intervals (CI) and 95% prediction intervals (PI). The risk of bias and quality of reporting in the studies were indicated by the Appraisal tool for Cross-Sectional Studies (AXIS). Results: 11 studies reporting on 13 associations were deemed eligible. The pooled effect size was moderate to large, 0.72 (95% C: 0.50-0.90; 95% PI: 0.02 to 1.41) with marked heterogeneity (Cochran's Q (df=12) =92.8, p<0.001; I 2 = 88.1%). Risk-of-bias appraisal showed that non-response bias was never addressed and the items associated with selection bias were only partially met. Conclusion: The moderate association between cognitive

reserve and cognitive performance suggests that building reserve could prove promising for HIV.

2-G-138 A simple protocol to use DiI for dendritic spine visualization in lightly fixed rat sections

Juan Trivino Paredes[1], Patrick Nahirney[1], Brian Christie[1]

[1]University of Victoria

Santiago Ramon y Cajal, used and improved a histological staining method initially developed by Camilo Golgi known as Golgi staining. This approach allowed him to create his famous hand drawings of several neuronal types with enormous quality. Despite its antiquity, it is still a widely used technique in neuroscience research. Besides Golgi staining, there are other approaches that have allowed to reveal the complex structure of cells in the nervous system. These other techniques include viral vector transfection, intracellular filling, electron microscopy and the use of transgenic animals. Another staining technique, originally described in 1986 and based on carbocyanine molecules, is gaining popularity again as an approach to study the neuronal structure. Carbocyanines are small lipophilic molecules that stain the plasma membrane through passive lateral diffusions and it has recently been used to analyze dendritic spines. Dendritic spines are small specialized subcellular membrane structures that receive most of the excitatory inputs in neurons. These structures play a crucial role in synaptic transmission and plasticity, and changes in their features can have a significant impact in these processes. Here we describe a simple and detailed protocol that combines DiI with confocal microscopy to label and visualize neurons in different brain regions and allows to analyze dendritic spine changes. Specifically, we show how this approach can be used to study dendritic spine alterations following a model of mTBI used in our research group.

2-G-139 Spontaneous Cortical Dynamics Revealed by High-Speed Voltage Imaging

Mark Reimers[1], Majid Mohajerani[2], Mike Moore[1], Javad Karimi[2], Sam Nola[1]

[1]Michigan State University, [2]University of Lethbridge

Neuroscientists have long sought to observe the dynamic brain in action. Mesoscopic optical imaging methods using rapid voltage indicators have the resolution to characterize these

dynamics, but these techniques don't yet reach their potential due to optical noise and pulse and neurovascular artifacts. We have developed methods to reduce the noise and artifacts in this rapid imaging modality, while preserving rapid transients. Applying our pre-processing methods to rapid voltage indicator data reveals rich cortical-cortical dynamics, which to our knowledge, have not been seen before in such detail. Some highlights are: 1. In lightly anesthetized (responsive but quiet) animals there are distinct periods of activity, lasting between 400ms and two seconds, interspersed with quiet periods of 1-3 sec, depending on the level of anesthesia, during each of which the cortex shows at least three distinct activity patterns, often starting in retrosplenial cortex (RSC). 2. In awake animals, we see different dynamics than in anesthetized animals. Delta-band activity is much less symmetric, and there is higher alpha-band activity, which is more symmetric across hemispheres. We have taken care to eliminate the pulse artifact from these data. 3. In some experiments, LFP was recorded from CA1 region of the right hippocampus. In both awake and lightly anesthetized animals, we see relationships between sharp-wave ripples (SWR) and patterns of cortical activity. We show that new technologies coupled with advanced preprocessing methods can bring into view rapid cortical dynamics.

2-G-140 Body movements triggered mesoscopic cortical activity in mice.

Matthieu Vanni[1], Dongsheng Xiao[1], Matilde Balbi[1], Jamie Boyd[1], Tim Murphy[1]

[1]University of British Columbia

Resting state spontaneous activity is commonly used to map the brain at mesoscale. With the recent development of mice expressing genetically encoded calcium indicators, cortical activity can be measured at high sensitivity in awake behaving animal. A new challenge is now the possibility to combine it with other modalities ranging different spatial and temporal scales. Here, we explored the arrangement of mesoscale spontaneous calcium activity in cortex with spontaneous motor action. Mice expressing the calcium indicator GCaMP6 were implanted with bilateral chronic window covering most of the dorsal cortex including motor, somatosensory and visual cortex. Green fluorescence was recorded in head fixed awake mice using a CCD camera. Body movement quantifications was performed using video tracking of paws, whiskers or pupils as well as the spontaneous locomotion on a treadmill by quantifying the density of movement (absolute sum of gradient between frames for each pixel). The fluorescence fluctuation associated with each individual movement was averaged and revealed specific cortical sequences of activity. Similar results were observed using cross-correlation between the density of movement and the calcium activity in each pixel. High correlations ($r>0.6$) were

observed in expected regions based on the somatotopic organization of the cortex such as whisker movements generating strong correlation in barrel and motor cortex. This approach opens new possibilities to easily probe the relationship between motor and brain function in a number of disease models.

2-G-141 A Novel Neuro-Rehabilitation Cooperative Journey: Incorporating Patient Input

Bonita Davidson[1]

[1]Vancouver Island University

The present paper outlines the findings of a 10-year case study that examined the effects of a novel co-operative rehabilitation plan that was developed for a 42 year old university professor who sustained a coup-contrecoup injury to her brain. Initially, when the professor struggled with acute symptoms in areas of speech, mobility, cognition, fatigue, headaches, dizziness, and confusion; she accepted a passive role in being rehabilitated. At three months, the professor began to read neurological-based research literature, and began to offer her own insights on her path of healing. She began to insist on a style of rehab with her practitioners (GP, neurologists, ENTs, physiotherapists, occupational therapists, vestibular rehabilitation therapists, and a speech and language pathologist) that was cooperative rather authoritative. Although some rehab plans involving her ideas were not successful, and appeared to cause notable setbacks in recovery; some plans did appear to be successful, such as the learning of foreign languages, studying new musical instruments, and daily riding a bike on a very curvy trail that aggravated her vestibular boundaries. The most notable observation was that she was an undeterred active participant in the planning of her own rehabilitation. 10 years from the date of injury, the patient recovered to a point at which her performance and intellect appear to be at or above her pre-injury state, as seen in many aspects of her life as a full-time professor, mother, and community volunteer.

2-G-143 Motion free micro-endoscopic system for imaging in freely behaving animals at variable focal depths using liquid crystal lenses.

Arutyun Bagramyan[1], Tigran Galstian[1], Armen Saghatelyan[2]

[1]University Laval, [2]CERVO Brain research center, Laval University

Imaging in freely behaving animals (FBA) have been so far limited to two-dimensional observations. We present a novel micro-endoscopic system, which combines fixed focal gradient index and tunable liquid crystal lenses (TLCL) technology to achieve a motion-free focal shift at a constant magnification. Custom four-layers design of the TLCL allowed to reduce system's optical aberrations and enabled polarization-independent imaging while maintaining a relatively low operation voltage, significantly improving the energy efficiency of the system and facilitating the transition to imminent, wireless approach. A focal shift of approximately 90 ± 3µm was achieved by electrically controlling the TLCL using the driving frequency at a constant voltage. While enabling 100% electrical depth imaging, developed micro-endoscopic system incorporates multiple mechanical advantages (size, weight, clipping system, etc.) and also presents a new optical design allowing high magnification imaging with a lateral resolution ≈ 1µm. The potential of our system to visualise and differentiate small neuronal structures at variable focal depth was tested by imaging neurons, dendrites and also spines in thick brain sections and also in vivo, in deep regions of adult mouse brain such as subventricular zone (SVZ) and rostral migratory stream (RMS). Our results indicate that the developed system is an efficient way for depth-variable imaging of fine morpho-functional properties of neural circuitries.

2-G-144 AAV-compatible MiniPromoters Delivered Intravenously Target Specific Cell Types of the Brain including the Cortex, Striatum, Dorsal Raphe, Locus Coeruleus, and Endothelial Cells of the Blood Brain Barrier

Andrea Korecki[1], Siu Ling Lam[1], Rachelle Farkas[1], Oriol Fornes[1], Anthony Mathelier[1], Wyeth Wasserman[1], Elizabeth Simpson[1]

[1]University of British Columbia

Small promoters (MiniPromoters) that drive cell-type restricted expression in the CNS are important tools for basic and clinical research, and may be critical for the success of future gene therapies. Such promoters will restrict expression and thus limit off-target side effects and immunogenicity, show a more physiological-like expression, and contain exclusively human sequences. Here, we have focused on the development of MiniPromoters for use in recombinant adeno-associated virus (rAAV). MiniPromoters either were new bioinformatics-driven designs from genes with therapeutically interesting expression patterns, or were further developed from our previous work. All promoters were cloned into a custom rAAV genome plasmid driving EmGFP (emerald GFP), and including an intron, WPRE (a transcript stabilizer), and SV40 polyA,

and then packaged into rAAV9. All viruses were tested by intravenous injection at 5E11 genome copies into neonatal B6129F1 mice. Expression was analysed after 4 weeks by cryosections for immuno detection of GFP, and for a subset of MiniPromoters with co-staining with relevant markers. Successful MiniPromoters ranged in size from 682 to 3,049 bp. Highlights include promoters derived from CLDN5 for the endothelial cells of the blood brain barrier, DBH for the locus coeruleus, FEV for the dorsal raphe, GPR88 for the striatum, and NOV for the cortex. All published MiniPromoters are available through Addgene (www.addgene.org), and unpublished materials are available by contacting Elizabeth M. Simpson (simpson@cmmt.ubc.ca).

2-G-145 On the Generalizability of Nonlinear Models of fMRI Data and the True Model Selection Problem

James Hughes[1], Mark Daley[1]

[1]University of Western Ontario

The human brain is a nonlinear system and yet the most popular and successful methods for modelling functional connectivity from fMRI data generate strictly linear models (Pearson correlation, general linear model). Although many contributions have been made with these linear models, they may lack the descriptive power required to articulate the "biologically true" functional connectivities. Genetic programming (GP), a type of machine learning, is used to perform symbolic regression --- a model-free regression analysis capable of dimensionality reduction and nonlinear model generation; it optimizes both parameters and model structure. GP is used to find mathematical expressions describing relationships in fMRI data. Symbolic regression is more powerful than, and makes fewer assumptions than, linear regression. fMRI data for forty subjects performing all tasks was obtained from the Human Connectome Project. Data was segmented into meaningful regions of interest (ROI) and nonlinear models of functional connectivity were generated. These nonlinear models contained fewer ROI when compared to linear models generated with traditional tools and were never significantly worse. Nonlinear models could not generalize to other subjects as well as linear models, but could better generalize to unseen data from the same subject. We also present the problem of selecting a model of functional connectivity when presented with a collection of different, but similarly effective, models.

2-G-147 Engineering next-generation optogenetic Pannexin-1 channels

Alexander Lohman[1], Robert Campbell[2], Roger Thompson[1]

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

Pannexin-1 (Panx1) forms large pore channels regulating synaptic plasticity, neuronal excitotoxicity and inflammatory signaling in the brain. Our understanding of Panx1 in neuro(patho)physiology has expanded since their discovery in 2000, but detailing the exact roles in these phenomena is limited by non-specific tools to isolate channel activity. Recently, we developed a first-generation light-controlled Panx1 channel (Opto-Panx1) that is irreversibly activated by cleaving the auto-regulatory C-terminal domain (4.65 min latency to activation). This tool has aided in defining the sufficiency and necessity of Panx1 in driving neuronal death during ischemic stroke. Due to the irreversible nature of Opto-Panx1, applications are limited to studying neuropathological paradigms. To fine-tune control of Panx1 activity, we engineered a new channel with improved temporal dynamics. The light-oxygen-voltage (LOV) domain from Avena sativa was cloned into the auto-regulatory C-terminal domain to create a library of chimeras. In the dark state, LOV2 has a structured Jα-helix folded atop an anti-parallel β-sheet "sandwiching" an FMN co-factor. Upon blue light (~450nm) illumination the Jα-helix unfolds and can be harnessed to impart conformational changes to regulate protein activity. The Jα-helix restructures into its folded confirmation in the dark state reversing any light-induced changes. Using Panx1 dye uptake assays, ATP release assays and whole-cell patch clamp electrophysiology, we identified a chimera (Panx1-LOV) with improved temporal control (35.2s latency to activation).

2-IBRO-148 Sex differences in the antiallodynic effect of L-655,708 correlate with Gabra5 expression in a model of neuropathic pain in rats

Úrzula Monserrat Franco-Enzástiga[1], Ana Belen Salinas-Abarca[1], Vinicio Granados-Soto[2]

[1]CINVESTAV, [2]Centro de Investigación y de Estudios Avanzados del I.P.N

α5-subunit containing GABAA receptors (α5GABAAR) have been shown to contribute to chronic pain. Gabra5, the gene coding for this subunit has been shown to be regulated by DNA methylation changes in the process of aging in rat hippocampus. Recent evidence indicates that positive allosteric modulators selective for α5GABAAR reduce stress-induced behaviors in a sex-dependent manner, suggesting that the role of these receptors in pain may depend on the sex. The aim of this study was to evaluate the sex differences in the antiallodynic effect of the

α5GABAAR inverse agonist L-655,708, Gabra5 regulation mediated by DNA methylation and α5GABAAR localization in DRG in rats subjected to L5/6 spinal nerve ligation (SNL). Nerve injured rats were treated with L-655,708 (0.15, 1.5 and 15 nmol/rat, i.t.) at 7, 14 and 21 days after SNL. Gabra5 mRNA and CpG island DNA methylation levels were determined at selected times by PCR and pyrosequencing, respectively. α5GABAAR localization was determined by immunofluorescence. L-655,708 produced a dose-dependent antiallodynic effect in female, but not male, rats. Nerve injury reduced Gabra5 mRNA expression in L5/6 DRGs in female and male rats, being greater in male rats. Nerve injury increased CpG DNA methylation percentage in L5/6 DRGs. Nerve injury also decreased α5GABAAR immunoreactivity in L5/6 DRGs 21 days post-surgery. Data suggest that blockade of spinal α5GABAAR induces a sex-dependent antiallodynic effect in neuropathic rats, which could be related to the sex-specific Gabra5 regulation changes in response to nerve injury.

2-IBRO-149 Mechanistic investigation of antimalarial drugs induced modulation of aggressive behavior using Drosophila melanogaster

Ahmed Adedeji[1], Sodiq Lawal[2], Magori Cassian[2]

[1]Department Of Pharmacology, Faculty Of Health Sciences, Habib Medical School, Islamic University In , [2]St.Francis University College Of Health And Allied Sciences

Objective: This was to evaluate antimalarial drugs for modulation of aggressive behavior in Drosophila melanogaster (DM) model. Method: DM specie (W118) was used in this study. Flies were divided into different experimental groups. Flies were exposed to chloroquin, quinine, Fansidar, Artesunate, and Artemether-lumefantrine. These were later on exposed to neurotransmitter modulators i.e. octopamine, dopamine, serotonin. Data was recorded in triplicate and analyzed using MS Excel and SPSS version 16. Information was presented in mean ± SEM and significance at 95% was considered. Result: The study showed that Artesunate had the highest effects of aggression in male DM flies while quinine and chloroquine were associated with low effects. Artemether-lumefantrine was associated with low level of aggression in female flies only. Fansidar and Artemether-lumefantrine acted synergistically to octopaminergic stimulation in both males and females respectively. Artesunate antagonized actions of promethazine leading to increased aggression especially in male flies. Fansidar and Artemether-lumefantrine acted synergistically to dopaminergic stimulation. Serotonin decreased aggression. Artesunate showed strong inhibitory activity on serotonin release, thus leading to increased aggression. In the age groups, aggression by Artesunate was highest in adult male

and female flies and this raises major pharmaceutical concerns. Conclusion: Molecular mechanism on actions of Artesunate and Fansidar on modulation of neurotransmitter release need to be investigated further to gain much clear insight.

2-IBRO-150 Redox homeostasis in brain of rats subjected to global perinatal asphyxia

Carolyne Lespay Lespay-Rebolledo[1], Ronald Perez-Lobos[1], Andrea Tapia-Bustos[1], Paola Morales[1], Mario Herrera-Marschitz[1]

[1]University of Chile

The present report evaluates the effect of global perinatal asphyxia on several parameters of oxidative stress in rat brain tissue sampled at an extended neonatal period up to 14 days. Perinatal asphyxia was induced by immersing foetus-containing uterine horns removed by a caesarean section from on term rat dams into a water bath at 37oC for 21 min. Brain samples (mesencephalon, telencephalon and hippocampus) were assayed for glutathione; catalase (Western blots and ELISA), and cleaved caspase-3 (Western blots) levels. It was found that global PA produced a regionally-specific and delayed increase in GSSG/GSH ratio; a regionally and time specific decrease of catalase activity and increase of cleaved caspase-3. The present study provides evidence for regionally impaired redox homeostasis in the brain of rats subjected to global PA, showing a delayed effect up to P14, mainly affecting mesencephalon and hippocampus, showing a sustained oxidative stress after the post-hypoxia period.

2-C-151 Disruption of the TAOK2 gene in human iPSC-derived neurons and its effect on neuron development and function

Nadeem Murtaza[1], Eric Deneault[2], Susan Walker[2], Ryan Yuen[2], Melanie Richter[3], Robin Scharrenberg[3], Birgit Schwanke[3], Froylan Calderon De Anda[3], James Ellis[4], Stephen Scherer[4], Karun Singh[1]

[1]McMaster University, [2]Sickkids Hospital, [3]University of Hamburg, [4]The Hospital for Sick Children

Altered neural connectivity is a major contributor to neurodevelopmental disorders (NDDs), including Autism spectrum disorder (ASD). Our recent publication (Richter and Murtaza et al. Molecular Psychiatry. 2018), describes the altered behaviour, brain morphology, and underlying deficits in cortical layering and synaptic function that are associated with pathophysiologies of

ASD and the 16p11.2 deletion. Whole genome sequencing of individuals with ASD further identified 2 de novo mutations that caused either gain-of-function or loss-of-function of TAOK2 and had differential effects on neuron development in the mouse brain. However, it is unknown whether the effect of knocking out TAOK2 or introducing the de novo variants will be recapitulated in the human neuron. To study the role of TAOK2 in the human context, we have generated human isogenic iPSC lines with knockout of TAOK2 or knock-in of the two de novo mutations. By differentiating these lines into human neurons we are studying alterations in neuronal morphology and activity, with preliminary results suggesting similar reduced basal synaptic activity as the mouse. We are also generating cortical spheroids to determine the effect on neural differentiation, migration and maturation in a 3D model that mimics human brain development. The objective of utilizing human iPSC-derived neurons will be to identify the altered human disease relevant molecular pathways and to create a platform for large-scale drug screening for identification of possible therapeutic targets.

2-A-152 Uncovering novel OTUD7A binding partners in the brain using the BioID2 system

Brianna Unda[1], Mohammed Uddin[2], Vickie Kwan[1], Nicholas Holzapfel[1], Nadeem Murtaza[1], Kristin Hope[1], Brad Doble[1], Jacob Nielsen[3], Stephen Scherer[4], Karun Singh[1]

[1]McMaster University, [2]Mohammed Bin Rashid University of Medicine and Health Sciences, [3]Lundbeck A/S, [4]The Hospital for Sick Children

The 15q13.3 microdeletion syndrome region contains up to ten genes and is associated with numerous neurodevelopmental disorders, 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)/ mice), previous work from our lab 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 outgrowth and dendritic spine formation. Additionally, an exonic de novo mutation in OTUD7A found in an ASD proband was found to impair OTUD7A function. However, the mechanism by with OTUD7A regulates cortical neuron morphology remains unknown. To study this, we are employing the BioID2 system to uncover novel OTUD7A binding partners in the brain. The BioID2 system makes use of a promiscuous biotin ligase which, when fused to a protein of interest, will biotinylate proteins within close proximity. These proteins can then be pulled down and subsequently identified through mass

spectrometry. We have created lentiviral constructs containing either WT OTUD7A or the exonic de novo OTUD7A mutant fused to BioID2, which will then be used to overexpress OTUD7A-BioID2 in mouse cortical neurons. These experiments will determine what proteins bind to OTUD7A in the brain and whether the ASD de novo mutation impacts any of these interactions.

3-A-1 The Molecular Mechanisms of Plexin-dependent Synaptic Tiling

Mizuki Kurashina[1], Akihiro Shibata[2], Hideji Murakoshi[2], Kota Mizumoto[1]

[1]University of British Columbia, [2]National Institute for Physiological Sciences

Precise movement requires proper, controlled innervation from neurons to their respective post-synaptic targets. In Caenorhabditis elegans, motor neurons form en passant synapses along the axon and each neuron forms unique synaptic domains innervating stereotyped muscle fields. Adjacent neurons from the same class form synapses domains in a tiled but non-overlapping pattern. We have previously found that Semaphorins and its receptor, Plexin (plx-1), is required to regulate tiled synaptic patterning in a set of DA class cholinergic motor neurons: DA8 and DA9. Here we found, rap-2/Ras GTPase and its effector mig-15/TNIK, function downstream of plx-1 to spatially restrict synapse patterning. Both rap-2 and mig-15 mutants show significant overlap between DA8 and DA9 synaptic domains. Fluorescent Lifetime Imaging microscopy (FLIM) revealed that PLX-1 locally restricts RAP-2 activity in the DA9 neuron, thereby restricting synapse formation at the synaptic tiling border. To understand the molecular mechanisms of Plexin-dependent synaptic tiling, we conducted forward genetic screening and identified a mutant (wy829) that showed the same synaptic tiling defects as plx-1. Genetic complementation test suggested that wy829 has a mutation in a previously unidentified gene. We will discuss about the identity of this novel gene as well as potential downstream mechanisms of Rap2/TNIK at the meeting.

3-A-2 Axonal tiling in D-type motor neurons

Ardalan Hendi[1], Kota Mizumoto[1]

[1]University of British Columbia

Precise patterning and innervation of neurons is essential for the proper functioning of the nervous system. Neuronal tiling is a phenomenon where axons and dendrites of neighboring

neurons of the same class communicate with each other to form complete but non-overlapping receptive fields. Previous studies of neuronal tiling in mammals and Drosophila suggested the diverse mechanisms of inter-neuronal interaction. Here, in order to understand the novel mechanisms of axonal tiling, we focus on the axonal tiling of the GABAergic motor neurons (DDs) in Caenorhabditis elegans. Previous electron microscopy has revealed that the axons and dendrites of DD neurons tile with each other. By using cell specific promoters and fluorescent proteins, we established a marker to visualize two neighboring DD neurons (DD5 and DD6). Using this marker strain, we found that axonal tiling between DD5 and DD6 is defective in egl-20/wnt mutants, whereby axons of the two adjacent neurons overlap significantly. Conversely, overexpression of egl-20/wnt causes further retraction of axons, suggesting that Wnts have a repulsive role in mediating axonal tiling. Furthermore, we found that the gap junction formed between DD5 and DD6 axons plays a role in establishing and maintaining axonal tiling. In the gap junction mutants, we observed a small but significant overlap between DD5 and DD6 axons, suggesting that gap junction proteins are required to restrict axon outgrowth beyond the tiling border. Taken together, we propose that Wnt signaling and gap junction proteins act in concert establish axonal tiling.

3-A-3 mab-9, a T-box transcription factor, is required for synaptic tiling in C. elegans

Jane Wang[1], Kota Mizumoto[1]

[1]University of British Columbia

The development of neural circuits requires the precise mapping of neurons at the synapse level. In Caenorhabditis elegans, synapses of the motor neurons are spatially organized in a phenomenon termed synaptic tiling, where adjacent neurons of the same class form their respective synapses in a continuous but non-overlapping manner. We have previously shown that the Semaphorin/Plexin signaling pathway regulates synaptic tiling in cholinergic motor neurons, but the mechanisms of this synapse patterning are still largely unknown. From an unbiased forward genetic screening, we found that loss of mutant of mab-9 caused severe synaptic tiling defects as observed in semaphorin and plexin mutants. In addition, the length of dendrite in these neurons was significantly shorter than wildtype. mab-9 belongs to a group of transcription factors which have a common DNA-binding domain (T-box) that is evolutionarily conserved across many species. mab-9 has been shown to determine cell fates in the hindgut and male tail. Surprisingly, cell fate of the cholinergic neuron was largely unaffected, suggesting that mab-9 can regulate neuronal patterning independently from its role in cell fate

determination. We are currently investigating the roles of mab-9 in the regulation of synaptic tiling.

3-A-4 TNIK/mig-15 is a negative regulator of synapse formation in C. elegans.

Ethan Fortes[1], Kota Mizumoto[2]

[1]Mr., [2]University of British Columbia

Fine motor coordination requires precise connectivity between motor neurons and their muscular targets. The nematode Caenorhabditis elegans is an excellent model organism to study the mechanisms of fine neuronal map formation at the synapse level due to its simple sinusoidal locomotion, simple and fully-characterized neuroanatomy. In C. elegans, motor neurons show unique tiled synaptic patterns where each axon of a given motor neuron class forms synapses in domains that do not overlap with those of their adjacent neurons, thus forming a complete synaptic field. We have previously shown that synaptic tiling between two cholinergic neurons, DA8 and DA9, requires the Semaphorin receptor Plexin (plx-1). We recently found that GTPase Rap2 (rap-2), and its effector Traf-2 and Nck-Interacting Kinase (TNIK/mig-15), act downstream of Plexin. We found that mig-15 is a negative regulator of synapse formation; mig-15 loss of function mutants show an increase in synapse number and over-expression of mig-15 in all neurons results in reduction of synapse number in all neurons and severely impairs locomotion. To understand the mechanisms of how mig-15 inhibits synapse formation, we conducted a suppressor screen of mig-15 overexpression. We isolated at least two genes that suppressed uncoordinated locomotion phenotype of mig-15 overexpression animals. We will discuss the functional characterization of these genes.

3-A-5 Wnt Signaling in Asymmetrical Neurite Pruning in C. elegans

Menghao Lu[1], Kota Mizumoto[1]

[1]University of British Columbia

Developmental neurite pruning is a phenomenon widely observed in different organisms including human. Through this process, neurons selectively remove exuberant neurites by pruning to form a proper neurocircuit. In human, half of the neural connections formed during embryonic stage are eliminated in the first two years of life. While many neurite pruning process

are activity-dependent, some neurons do undergo stereotyped pruning, such as Drosophila sensory neurons, suggesting the role of morphogenic cues in neurite pruning. We found that in Caenorhabditis elegans, a cholinergic motor neuron, PDB, undergoes stereotyped neurite pruning. During PDB development, we observed two posterior branches that are not present after PDB development. Time-lapse imaging showed that these posterior branches are pruned while the anterior branch is extending. We also found a posteriorly expressed Wnt, LIN-44, is responsible for the pruning of the posterior neurites. In lin-44/Wnt mutants, the posterior neurites failed to be pruned, resulting in the ectopic branch residue. LIN-17, a Frizzled receptor for LIN-44, was localized at the tip of the posterior pruning neurites but not in the anterior neurites. This asymmetric localization of LIN-17 was dependent on LIN-44(Wnt). Wnt signaling is known to act as an axon repellent cue during neuronal development. Our results showed a novel role of Wnt in asymmetric neurite pruning.

3-A-6 The role of MDGA proteins in regulation of neuroligin-neurexin signaling

Vedrana Cvetkovska[1], Jonathan Elegheert[2], Ina Ammendrup-Johnsen[1], Daiki Ojima[3], Steven Connor[4], Amber Clayton[2], Yicheng Xie[1], Tohru Yamamoto[3], Radu Aricescu[2], Ann Marie Craig[1]

[1]University of British Columbia, [2]University of Oxford, [3]Kagawa University, [4]York University

Neuroligin-neurexin (NL-NRX) complexes are fundamental synaptic organizers in the central nervous system. An accurate spatial and temporal control of NL-NRX signaling is crucial to balance excitatory and inhibitory neurotransmission. MAM domain containing glycosylphosphatidylinositol anchor 1 (MDGA1) was first reported to bind NL2 and negatively regulate inhibitory synapses, while MDGA2 was reported to bind NL1 and NL2 and regulate excitatory synapses. How MDGA proteins bind NLs and control their function is unclear. We described crystal structures of MDGA1 and the NL1-MDGA1 complex. Two MDGA molecules fold into rigid triangular structures, cradling a dimeric NL to prevent NRX binding. We find that MDGAs can bind all NLs with varying affinities, and can suppress synapse formation in a co-culture assay in an expression level and NL splicing-modulated fashion. Through structural analysis we designed NLs that are insensitive to MDGA inhibition without affecting NRX binding, and rationalize the impact of autism-linked NL3 R451C mutation, where NL3 loses the ability to interact with MDGA1. We show that MDGA1 is selectively expressed by excitatory neurons in hippocampus and cortex and is absent from interneurons, while MDGA2 is expressed in subtypes of excitatory and inhibitory neurons. These results illustrate a potentially brain-wide regulatory mechanism for NL-NRX signaling by MDGAs, where expression levels in particular cell

types could explain MDGA1 and MDGA2 selectivity for modulation of inhibitory and excitatory neurotransmission.

3-A-7 Gap junctions are required for glia-glia communication, calcium signaling and survival in the Drosophila peripheral nerve

Mriga Das[1], Till Matzat[1], Vanessa Auld[1]

[1]University of British Columbia

To ensure proper neuronal signaling, Drosophila peripheral axons are surrounded by three glial layers; the wrapping glia (WG) that directly contacts axons, the subperineurial glia (SPG) that acts as a barrier through the formation of septate junctions and the perineurial glia (PG) that surrounds the entire nerve. Extensive communication between these layers is required for proper development of peripheral nerves as they undergo extensive growth and differentiation. The mechanisms underlying glia-glia communication in these non-myelinating classes of glia however remain unknown. Here we show that a gap junction protein, Innexin 2 (Inx2) is present in all three glial layers. Similar to inx2 null mutants, which are embryonic lethal, knockdown of Inx2 in peripheral glia leads to lethality during larval stages. To determine which glial layers require Inx2, we knocked down Inx2 in individual glial layers. Loss of Inx2 channel function in the SPG results in the fragmentation and death of WG, suggesting a role for Inx2 in mediating SPG-WG communication and WG survival. To test if Ca2+ mediates SPG-WG communication, we imaged calcium signals in peripheral glia using the GCaMP sensors. Ca2+ waves are present in both the SPG and the WG of wild type larvae whereas these waves are absent after Inx2 knockdown in the SPG but not the WG. Altering calcium levels in the larva however, does not affect WG survival. In summary we propose that Inx2 mediates communication between the SPG and the WG through an unknown mechanism required for the survival of the WG.

3-A-8 APP in developmental axonal pruning

Andres de Leon[1], Julien Gibon[2], Philip Barker[2]

[1]McGill University, [2]University of British Columbia - Okanagan

Axon pruning is required for establishing and refining neuronal connections during development and for driving plasticity in the adult nervous system. Aberrant axon pruning

occurs in several neurological diseases and occurs well before neuronal cell body death takes place. The amyloid precursor protein (APP) has been reported to be actively involved in physiological axonal pruning. However its role has been controversial, with some studies showing a protective role for APP and others claining it is pro-degenerative. In the present study, we test the hypothesis that APP mediates developmental pruning of sensory neuron axons in development by characterizing animals rendered null for APP. We found evidence of supernumerary sensory neurons in APP-deficient animals, evidenced by an increase in the number of sciatic nerve axons. The effect of APP was then addressed using compartmentalized culture devices that permit cell body circumstances to be isolated from from axonal molecular mechanisms. With this approach, we found APP-null dorsal root ganglia (DRG) axons were highly resistant to local pruning induced within microdevice cultures. Together, our results indicate that APP has an active pro-degenerative role, driving local axon pruning in peripheral sensory neurons.

3-A-9 Calcium signaling determines the transition from quiescent to proliferative states of neural stem cell of the adult brain.

Archana Gengatharan[1], Marina Snapyan[1], Marie-Anne Lebel-Cormier[1], Magdalena Gotz[2], Armen Saghatelyan[3]

[1]CERVO Brain Research Center, [2]Institute for Stem Cell Research, National Research Center for Environmental Health, [3]CERVO Brain research center, Laval University

Neural stem cells (NSC) persist in the subventricular zone of adult brain and transit from the quiescent to the proliferative states to produce new neurons. The mechanisms regulating the transition from quiescent to proliferative states remain unclear. We aimed to study the division of NSC in freely behaving mice using miniature microendoscopes. To label NSC, we electroporated CAG-GFP plasmid postnatally and analyzed GFP-retaining cells in the adult brain. Immunohistochemical characterisation of label-retaining cells in the adult brain revealed that GFP-retaining cells are either non-diving astrocytes or NSC. Continuous imaging of NSC in freely behaving animal during 3 days revealed the lengths of NSC division is 81 ±18.1 min. Since adult NSC are enriched in genes involved in the calcium signaling, we next aimed to determine whether the transition from the quiescent to the proliferative state is calcium dependant. We electroporated calcium indicator GCaMP6s and performed calcium imaging in GCaMP6s-retaining NSC. Our data revealed that quiescent NSC display higher calcium frequency as compared to proliferative NSC. Application of 2-APB, IP3 receptor antagonist, decreased the

frequency of calcium events in quiescent NSC and fostered their entry into the proliferative state. Similarly, CRISPR-Cas9 editing of ITPR2 gene specifically in NSC increased their proliferation. Our data suggest that calcium signaling via IP3 sensitives stores plays an important role in the transition from quiescent to proliferative states of NSC.

3-A-10 Pleiotrophin reduces chondroitin sulfate proteoglycan mediated inhibition of neurite growth via anaplastic lymphoma kinase

Anna Wiersma[1], Somnath Gupta[1], Ian Winship[1], Kathryn Todd[1]

[1]University of Alberta

After CNS injury such as ischemic stroke, chondroitin sulphate proteoglycans (CSPGs) released by glial cells in the extracellular matrix surrounding the injury act to inhibit axonal growth and impair recovery. Pleiotrophin (PTN) is a growth factor and a cytokine that is upregulated in the central nervous system (CNS) during development and after injury. It has been proposed that PTN binds to CSPGs in the extracellular matrix, reducing CSPG inhibition of neuronal growth. However, the interactions between PTN and key regulators of neurite extension are not well described. Here, we investigated the direct regulation of neurite outgrowth in different neuronal cells (human neuroblastoma cell line-SH-SY5Y, rat neuroblastoma cell line-B35 and primary rat neuronal cultures) in vitro at various PTN concentrations. Cells were plated on growth inhibitory CSPG matrices or growth permissive laminin matrices. PTN increased neurite outgrowth in CSPG matrices only, and had no effect on neurite outgrowth in matrices with laminin. These data confirm that PTN increases neurite extension in inhibitory environments. Because these effects could result from interfering with CSPG-CSPG receptor interactions or by PTN activation of the anaplastic lymphoma kinase (ALK) receptor, further studies were performed in primary cultures treated with PTN with or without ALK inhibitor alectinib. Data from these inhibitor studies suggests that ALK activity is important to promote growth by PTN. Combined, these data further validate PTN as a potential pro-plasticity therapy following CNS injury.

3-A-11 TNF pathway genes in Drosophila sensory neuron development

Charlene Hoi[1], Wenjing Ruan[2], Redouane Allache[2], Philip Barker[3]

[1]University of British Columbia, Okanagan Campus, [2]McGill University, [3]University of British Columbia - Okanagan

Neurodevelopment involves growth, pruning, and reformation of neuronal processes. These events are regulated by signaling pathways that can lead to neurodegenerative disorders when dysregulated. Our knowledge of the signaling mechanisms regulating degenerative pathways is rudimentary and deeper understanding of these processes is required to identify viable therapeutic targets. Mammalian Tumor Necrosis Factor (TNF) receptors have been implicated in neurodegeneration, but the signaling events that allow these receptors to mediate degeneration remain unclear. Mammals possess ~30 TNF receptors whereas Drosophila have only two: wengen (wgn) and grindelwald (grnd). To date, characterization of wgn and grnd has focused on induction of cell death by overexpression of eiger (egr), the sole Drosophila TNF ligand, or on their roles in innate immunity, cell proliferation, and cell competition. Here, we have analyzed the role of egr, wgn and grnd in Drosophila ddaC sensory neuron development and pruning. Our data indicate that wgn and grnd have distinct roles in sensory dendrite growth, pruning, and debris clearance. Intriguingly, egr does not appear to be required in these processes, suggesting egr-independent functions for wgn and grnd. Given that most aspects of TNF signaling have been conserved from invertebrates to vertebrates, analysis of signaling events that allow egr, wgn, and grnd to regulate ddaC development and pruning will shed new light on analogous processes in mammals, informing us on potential therapeutic targets for TNF-associated neurodegenerative disorders.

3-A-12 Axon degeneration requires cytosolic Ca2+ influx through TrpV1

Aaron Johnstone[1], Philip Barker[2]

[1]Montreal Neurological Hospital/ McGill University, [2]University of British Columbia - Okanagan

Neurite pruning and neuronal cell death occur normally during embryonic development to establish and refine the maturing nervous system, but components of the same destructive signaling pathways appear to underlie neurodegenerative diseases such as Alzheimer's, Parkinson's and ALS when aberrantly reactivated in adulthood. The emerging overlap between developmental and pathological mechanisms of neurodegeneration strongly suggests that therapeutic opportunities can be revealed by understanding the sequence of molecular events culminating in degeneration of neurites and entire neurons. Developmental degenerative signaling is modeled in vitro by nerve growth factor (NGF) withdrawal from DRG neurons, though many key aspects the signaling process underlying degeneration remains obscure. We

report that NGF deprivation from DRG sensory neurons induces a robust increase in axonal Ca2+ prior to membrane blebbing and degeneration. Chelation by EDTA robustly rescues axons from degeneration and degeneration is significantly rescued by pharmacological inhibitors of calcium channels. Cultured sensory neurons derived from TrpV1-null mouse embryos indicate a pro-degenerative role for TrpV1 downstream of PKC and reactive oxygen species.

3-A-13 Changes in laterality of spinofugal projections caused by spinal cord deletion of DCC during development

Farin Bourojeni[1], Ronan da Silva[1], Isobel Orfi[1], Hanns Zeilhofer[2], Artur Kania[1]

[1]IRCM (Institut de recherches cliniques de Montreal), [2]Swiss Federal Institute of Technology

Sensory information from the body channeled via spinal projection neurons (SPNs) to supraspinal centres generates appropriate motor responses. A significant number of SPNs are commissural such that their axons cross the spinal midline to innervate contralateral targets in the brain. The identity of axon guidance cues that orchestrate midline crossing and the development of spinofugal connections is unknown. We have recently shown that DCC, the netrin-1 receptor, is required for the development of the spinothalamic tract in mice. However, the role of DCC in guiding other classes of SPNs is unknown. First, we characterised the identity of SPNs that express the spinal cord-specific Cre driver Hoxb8::Cre via a Cre-depedent axonal TdTomato reporter. Subsequently, we performed a series of anterograde tracings via spinal cord injection of virally-driven synaptic-bound eYFP of spinal cord-specific Dcc knockout mice (Hoxb8::Cre; DCC[flox/-]) and their control littermates. Here, we demonstrate that in addition to the spinothalamic connections, the commissural nature of spinoreticular and spinomesencephalic tracts is also altered. In control animals, most observed synapses of such projections are contralateral to the spinal injection. In contrast, in Hoxb8::Cre; DCC[flox/-] mutants, detection of eYFP is significantly increased in the ipsilateral brain targets. Collectively, our results suggest that many SPN classes rely on DCC for crossing the nervous system midline before reaching their brain targets.

3-A-14 Role of the msxC gene in stem cell populations of the CNS during development and regeneration

Benjamin Lindsey[1], David Zheng[1], Shei Keil[1], Selena Do[1], Marie-Andree Akimenko[1], Tuan Bui[1]

[1]University of Ottawa

The mechanisms controlling stem cell behaviour during central nervous system (CNS) development and regeneration are poorly understood. Uncovering vertebrate-wide molecular programs regulating neural stem cell function will allow us to identify factors required for proper CNS patterning to prevent developmental disorders, and for successful CNS regeneration following brain and spinal cord injury. The zebrafish homeobox gene msxC, and its rodent ortholog, Msx3, are essential for dorsal neural tube patterning. In adult zebrafish, msxC is critical for successful fin regeneration. We identified a 1.5 kb cis -acting regulatory element (1.5CRE) 5' of msxC that is active in the zebrafish spinal cord and brain. In this study, we investigated the 1.5CRE activity in defined stem cell populations of the brain and spinal cord over ontogeny and its role following injury. Using cell cycle assays and stem cell marker analysis in our transgenic zebrafish line Tg(1.5CRE-βG:eGFP), we reveal that the 1.5CRE activity in the developing and mature spinal cord is present in subpopulations of radial-glial cells and in distinct neurogenic domains of the mid- and hindbrain. These findings suggest the possibility that 1.5CRE may be implicated in the differential regulation of diverse stem cell populations. We further examined the GFP expression pattern of the 1.5CRE activity upon CNS injury using established adult spinal cord and brain lesion assays. We propose the 1.5CRE as an important regulator of stem cell behaviour during CNS growth and during the regenerative process following neurotrauma.

3-A-15 The role of microglia in the adult olfactory bulb

Sarah Malvaut[1], Jasna Kriz[1], Armen Saghatelyan[1]

[1]CERVO Brain research center, Laval University

Microglial cells are resident immune cells of the central nervous system and play an important role under both physiological and pathological conditions. Here we studied the role of microglia in the adult olfactory bulb (OB). Using a bioluminescence approach and a TLR2-luciferase reporter mouse model, we showed a high level of microglia activation under normal conditions in the OB. This was confirmed with an immunohistochemical labelling targeting both Iba1 and CD68, markers of microglial cells and microglia activation, respectively. To understand whether microglia could be involved in olfactory processing and be activated following particular olfactory tasks we used bioluminescence and immunohistochemistry for CD68 and Iba1 following a novel odor stimulation, an olfactory enrichment and a go/no-go odor discrimination task. We next performed in vivo two-photon imaging of microglia in CX3CR1-GFP mice to follow their dynamics under baseline conditions and following odor stimulation. Altogether, our data

revealed that OB microglia are present in a highly activated state, have very dynamic processes and may migrate substantial distances under baseline conditions and following an odor stimulation.

3-A-16 Pre-adolescent Oxytocin Treatment Increases Social Investigation Dependent on Sex and Maternal Fluoxetine Exposure

Nicole Minielly[1], Wansu Qiu[1], Natasha Black[1], Jared Splinter[1], Paula Duarte-Guterman[1], Liisa Galea[1]

[1]University of British Columbia

Postpartum depression (PPD) affects approximately 10-15% of mothers. Selective serotonin reuptake inhibitors (SSRI's) are often prescribed to treat PPD, however, past research shows SSRI's enter breast milk, thereby exposing the infant. Previous studies find fluoxetine (FLX), an SSRI, adversely affects offspring development, including increased rates of anxiety and Autism Spectrum Disorder (ASD). ASD is a host of disorders involving social behaviour deficits. Intra-nasal oxytocin is being tested to relieve these deficits. This study used a corticosterone (CORT) induced rodent model of PPD, concurrently treated with FLX. The purpose was to determine maternal CORT and/or FLX effects on offspring development, and if any social deficits can be relieved with pre-adolescent offspring oxytocin administration. We hypothesized FLX would alter offspring anxiety and social behaviour, which would be mitigated by oxytocin. CORT and/or FLX were administered to the dams (postnatal day(PD) 2-23). Oxytocin and TriozanTM, a drug delivery system to facilitate large peptides across the blood brain barrier, were administered to the offspring (PD 25-34). Social behaviour, and anxiety testing were conducted (PD 35-37, and 70-73). Among the maternal FLX exposed offspring, females given preadolescent oxytocin +TriozanTM exhibited more social investigation. Males exhibited more social investigation than females, after maternal FLX. These data suggest TriozanTM improves oxytocin's efficacy, when administered peripherally. Unexpectedly, maternal CORT and FLX decreased offspring anxiety in adulthood.

3-A-17 Rostrocaudal differences within developing spinal locomotor networks in larval zebrafish (Danio rerio)

Melissa Paradis[1], Tuan Bui[1], Yann Roussel[1]

[1]University of Ottawa

During development, the gradual refinement of motor circuits enables mature movements to emerge. This is exemplified in the maturation of spinal circuits that lead neonates to learn to walk properly. While spinal locomotor circuits are already active during embryonic stages, they undergo changes that lead to mature forms of locomotion. Understanding these changes provides insights into how mature spinal locomotor circuits operate. Preliminary data suggests that in larval zebrafish, the development of spinal locomotor networks involves a transition from a pacemaker-driven electrical scaffold to network oscillators relying on chemical neurotransmission. However, neural development in the developing zebrafish occurs mainly along a rostrocaudal gradient and therefore, we asked whether the development of spinal locomotor circuits also occurs at different rates along the length of the spinal cord. Using electrophysiological recordings of the larval zebrafish spinal cord, we show that the transition from pacemaker to network-driven spinal locomotor networks occurs earliest in the caudal regions of the spinal cord. To further investigate the neural basis behind this phenomenon, images of select spinal neuron populations were visualized at the rostral and caudal ends of the spinal cord via the use of transgenic larval zebrafish. The connectivity of these spinal locomotor circuits at both ends was further described by the use of retrograde labelling. Our results suggest the existence of a spatiotemporal gradient in the incorporation of more mature spinal locomotor networks.

3-A-18 Transcriptome of subfornical organ is altered by early postnatal overnutrition

Colleen Peterson[1], Shuo Huang[2], Samantha Lee[1], Alastair Ferguson[3], William Fry[1]

[1]University of Manitoba, [2]University of Calgary, [3]Queen's University

Early postnatal overnutrition is associated the development of sequelae including obesity, type-II diabetes, and cardiovascular disease. Moreover, research on hypothalamic neurons in postnatally overfed rodent models show altered anatomy and response to energy balance signals. However, despite the role of the subfornical organ (SFO), a forebrain sensory circumventricular organ, in energy balance and cardiovascular output, no research has yet examined the response of the SFO to early postnatal overnutrition. Using the small litter model of postnatal overnutrition, we performed whole transcriptome sequencing on SFO tissue from rats from small (4 per litter), and control (large, 12 per litter) litters. The resulting read sequences were aligned to the Rat Rnor_6.0 genome, and control litter transcript frequency compared to a previously published microarray SFO data set for validation. Differential expression analysis

found statistically significant ($p<0.05$) changes in expression of 12 transcripts, including Manf, Slc24a4, and Cracr2b, which have known roles in neuronal excitability, neurite outgrowth and differentiation, and food intake. Furthermore, KOBAS gene ontology analysis identified a trend among significantly altered transcripts in roles for oxidative stress response. We recommend further investigation of these 12 transcripts in the SFO, and of the effect of early postnatal overnutrition on SFO physiology and morphology.

3-A-19 The influence of cortical morphology on bold signal variability

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

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

The brain is inherently a dynamic structure that is required to undergo fast moment-to-moment reconfigurations. Recent studies suggest that greater variability in brain signals (i.e. blood oxygen level-dependent signal variability - BOLD-SD) correlates with superior memory, cognitive performance and flexibility highlighting BOLD-SD as a new correlate of brain health in aging. However, it is possible that alterations in cortical morphology across the lifespan may be physiological confounds to the reported age differences in BOLD-SD. Aging is known to be associated with global cortical thinning (CT), grey matter loss (GM), and changes in cortical surface area (SA), yet their contribution to BOLD-SD remains unknown. We examined the influence of neuroanatomical alternations on BOLD-SD, in a longitudinal study (2 scans ~2.5 years apart) of 31 older subjects. A linear mixed model was used to determine differences in BOLD-SD across time. Then, CT, GM, SA were introduced as covariates in separate models. Lower BOLD signal variability values were found in the inferior occipital gyrus and sulcus, left subcallosal gyrus, inferior temporal gyrus and sulcus, collateral sulcus, lateral occipito-temporal sulcus, right medial orbital sulcus. These results were robust to GM and SA but not CT. After introducing CT as a covariate lateral occipito-temporal gyrus was significant, while subcallosal gyrus, and left inferior temporal gyrus lost significance. These findings suggest that CT is a physiological confound, and anatomical factors be taken into account when interpreting BOLD-SD studies.

3-A-20 Guidance and beyond: Roles for axon guidance genes in the adult nervous system

Aarya Vaikakkara Chithran[1], Douglas Allan[1], Timothy O'Connor[1]

[1]University of British Columbia

Axon guidance cues are extracellular signals that direct the growth and steering of neuronal growth cones. Both attractive and repellent cues are required to guide developing axons to their targets. Nonetheless, after axons have reached their targets and established functional circuits, expression of many guidance cues is maintained. In Drosophila, more than 96% of the embryonic guidance cues are expressed in the adult. The expression of these genes in the adult indicates that they have additional roles beyond the initial phase of neuronal process outgrowth, growth cone navigation, and target innervation. To examine the function of axon guidance genes in the adult nervous system, we performed an RNAi screen. Using bioinformatics tools, we identified 151 axon guidance genes that are expressed in adult Drosophila nervous system. We prioritized 44 genes based on their higher expression profiles and previously known roles in neuronal pathfinding. We knocked down these genes using spatial and temporal control of the GAL4-UAS system and identified 15 genes that are required for adult survival. We performed behavioral assays and found that loss of these 15 guidance cues caused motility defects and altered activity in adult flies. To understand the impact at a cellular level, we examined the effect of knocking down Fascicilin 3, an Ig containing homophilic cell adhesion molecule. We found that knocking down Fascicilin 3 led to death of a subset of neurons around the adult antennal lobe. We rescued this phenotype by preventing apoptosis with the expression of P35.

3-B-21 Structure-function analysis of Pannexin-1's permeability to anandamide

Connor Anderson[1], Allison Werner[1], Alex Lohman[1], Roger Thompson[1]

[1]University of Calgary

Pannexin-1 (Panx1) is a non-selective ion and metabolite permeable channel with broad tissue expression, including in excitatory neurons in the central nervous system. Although Panx1 is best known for its pathological roles, we recently described a novel role of Panx1 in regulating tissue levels of the endocannabinoid, anandamide (AEA). This occurs by Panx1 facilitating synaptic clearance of AEA. We hypothesize that Panx1 functions as an AEA permeable channel that regulates fast uptake of AEA into neurons. To test this, we generated single point mutations of amino acids that are predicted to line Panx1's pore region to polar serine residues. Using a combination of cell-attached single channel recordings and fluorescent dye (sulforhodamine 101) flux through single channels, we are investigating if there is a site-specific requirement of

pore-lining amino acids for AEA flux through Panx1. This will be accomplished using HEK293 cells transfected with Panx1 mutants. We predict that mutating single or multiple hydrophobic amino acids will alter the AEA permeability of Panx1. Thus, a detailed analysis of Panx1's apparent lipid permeability will establish a structure/function level of understanding the novel role of Panx1 as an endocannabinoid clearance pathway.

3-B-22 Contribution of Pannexin-1 to 4-AP Seizures in Mouse Neocortex

Mark Aquilino[1], Paige Whyte-Fagundes[2], Georg Zoidl[2], Berj Bardakjian[1], Peter Carlen[3]

[1]University of Toronto, [2]York University, [3]University Health Network

Pannexin-1 (Panx1) has been shown to have a vital role in modulating neuronal excitability and in acute neurodegenerative changes. Through quantitative analysis of electrophysiological properties of C57Bl/6 mice with Panx1 either pharmacologically blocked or knocked out, new evidence into the dependence of the 4AP seizure model on Panx1 function is presented. Whole-cell in vitro patch clamp recordings of pyramidal neurons from cortical layers II & III has revealed possible Panx1-null phenotypes, including persistent hyperpolarized resting membrane potential, and reduced excitability in response to 4AP. This suggests that Panx1 may play a role in maintaining neuronal excitability, and may be of interest in pathological hyperexcitability. This research provides a valuable tool for understanding the importance of Panx1 in physiological conditions, and quantifies its effects on neuronal excitability.

3-B-23 A spike timing-dependent plasticity rule for single, clustered and distributed dendritic spines

Roberto Araya[1], Sabrina Tazerart[1], Diana Mitchell[1], Soledad Miranda-Rottmann[1]

[1]Université de Montréal

Until now our understanding of spike timing-dependent plasticity (STDP) learning rules has come from studies using connected neuronal pairs or by using extracellular stimulating electrodes, where the precise location and structural organization of excitatory inputs capable of supporting STDP were unknown. Here we developed a protocol to induce synapse-specific STDP by means of two-photon uncaging of glutamate at single dendritic spines - to mimic synaptic release - preceded or followed in time by a backpropagating action potential to trigger spike

timing-dependent long-term potentiation (t-LTP) or depression (t-LTD), respectively. We now provide evidence for the role that the precise structural organization of excitatory inputs onto clustered (< 30 µm apart) or distributed (separated by > 30 µm) dendritic spines have on the generation of STDP, and the morphological and molecular mechanisms responsible for the induction of plasticity in single dendritic spines.

3-B-24 A T-type calcium-activated signaling cascade for CREB activation

Hadhimulya Asmara[1], Xiaoqin Zhan[1], Giriraj Sahu[1], Peter Stys[1], Gerald Zamponi[1], Raymond Turner[1]

[1]University of Calgary

Calmodulin (CaM) is an important signalling molecule that regulates high voltage-activated calcium channels and second messenger cascades that lead to gene transcription. Low voltage-activated calcium channels of the Cav3 family have the important role of mediating low threshold calcium influx, but were not believed to interact with CaM. We reported a constitutive association between CaM and the Cav3.1 (T-type) channel at rest that is lost through an activity- and Cav3 calcium-dependent CaM dissociation, and an associated activation of αCaMKII. Recent work has revealed a Cav3.1 channel-dependent LTP of parallel fiber input to Purkinje cells that we find can be triggered by optogenetic stimulation of parvalbumin-ChR2 expressing Purkinje cells in vitro. We now show under resting conditions a higher level of activated CaMKIV than αCaMKII in Purkinje cells, with membrane depolarizations increasing αCaMKII but decreasing CaMKIV. Depolarizations or optogenetic stimulation further trigger nuclear CREB activation. All changes in αCaMKII, CaMKIV, and CREB expression are blocked in the presence of the Cav3 calcium channel blocker TTA-P2. Our findings thus establish that Cav3-mediated calcium influx differentially regulates αCaMKII and CaMKIV levels during activation of a signaling cascade that triggers CREB in relation to long term plasticity of a major excitatory input to cerebellum.

3-B-26 Gamma oscillations in the rodent anterior limbic system: local generation or external source?

James Carmichael[1], Matthew Yuen[1], Matthijs van der Meer[1]

[1]Dartmouth College

Oscillations in the local field potential (LFP) are thought to reflect aspects of information processing, such as the gating or binding of information between anatomically distant brain regions. In the rodent limbic system, interconnected regions such as the prefrontal cortex (PFC), orbitofrontal cortex (OFC), nucleus accumbens (NAc), and cingulate cortex (CG), show coherent oscillations and spike-field relationships in various frequency bands, which may mediate the flow of information between these areas. Our previous work (Carmichael et al., 2017) has shown that inactivation of the piriform cortex (PC) by unilateral naris occlusion abolishes gamma oscillations in the ipsilateral NAc LFP . To determine how far into adjacent structures PC oscillations continue to dominate the LFP, we recorded LFPs from rats (n = 7) implanted with electrodes in OFC, vStr, PFC, and CG, as they underwent reversible unilateral naris occlusions. vStr and OFC showed a strong suppression in gamma power only when the ipsilateral naris was blocked, suggesting that local gamma oscillations in these structures are likely volume-conducted from the adjacent PC, while PFC and CG did not. Thus, gamma oscillations seen in brain regions adjacent to the PC are likely not generated locally; however, the influence of PC gamma does not extend to more distal areas. This emerging view of gamma oscillations in ventro-lateral limbic circuits highlights the importance of the common PC input as a major influence.

3-B-27 Acute photoinactivation of a cGMP-dependent protein kinase reveals distinct functions in nerve terminal growth and synaptic vesicle cycling

Jeffrey Dason[1], Aaron Allen[2], Oscar Vasquez[2], Marla Sokolowski[2]

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

Sustained neurotransmission requires the tight coupling of synaptic vesicle (SV) exocytosis and endocytosis. The mechanisms underlying this coupling are poorly understood. We tested the hypothesis that a cGMP-dependent protein kinase (PKG), encoded by the foraging (for) gene in Drosophila melanogaster, is critical for this process using a for null mutant, genomic rescues, and tissue specific rescues. We uncoupled FOR's exocytic and endocytic functions in neurotransmission using a temperature-sensitive shibire mutant in conjunction with fluorescein-assisted light inactivation of FOR. We discovered a dual role for presynaptic FOR, where FOR inhibits exocytosis during low frequency stimulation by negatively regulating presynaptic Ca2+ entry and facilitates endocytosis during high frequency stimulation through PIP2 signaling. Additionally, glial FOR negatively regulates nerve terminal growth and this developmental effect was independent from FOR's effects on neurotransmission. Overall, FOR plays a critical role in

coupling SV exocytosis and endocytosis, thereby balancing these two components to maintain sustained neurotransmission.

3-B-28 Influence of Neurexin 1 and PTPsigma on the formation of synapses established by dopaminergic neurons

Charles Ducrot[1], Charlotte Michaud-Tardif[1], Anne-Sophie Racine[1], Samuel Burke-Nani[1], Marie-Josée Bourque[1], Gisselle Correa[1], Guillaume Fortin[1], Louis-Eric Trudeau[1]

[1]Université de Montréal

Dopamine (DA) neurons of the substantia nigra compacta (SNc) and ventral tegmental area (VTA) establish a complex axonal arborization comprising axon terminals that appear to be mainly non-synaptic in structure, as revealed by ultrastructural observations. Our objective was to determine the synaptic proteins involved in synapse formation by DA neurons. It is now well established that the development of synaptic contacts implicates a set of specific trans-synaptic proteins including neurexins, neuroligins, PTP-S (protein tyrosine phosphatase type sigma) or TkrB (tyrosine kinase receptor B). We developed an in vitro system with primary DA neurons prepared from the SNc or VTA of tyrosine hydroxylase (TH)-GFP transgenic mice and placed in co-culture with neurons from dorsal or ventral striatum, respectively. Immunocytochemistry and confocal microscopy were used to examine the colocalization of presynaptic markers like VMAT2 and postsynaptic markers including PSD95 or Gephyrin. Then, using a viral approach we overexpressed and downregulated some of the genes in primary DA neurons. Our preliminary results show that, similarly to in vivo, cultured DA neurons establish a majority of non-synaptic terminals. We find that overexpression of Neurexin1 but not Neurexin 3 increases the formation of synapses established by VTA DA neurons by approximately 50% . We also find that downregulation of PTP-S decreases the proportion of synaptic contacts established by SNc DA neurons. These results suggest a fundamental role of Neurexin 1 and PTP-S in the formation of DA synapses.

3-B-29 Fxr1 regulates homeostatic synaptic plasticity through changes in AMPAR composition

Alesya Evstratova[1], Jivan Khlghatyan[2], Aleksandra Marakhovskaia[1], Tiago Silva[1], Simon Chamberland[3], Valerie Mongrain[4], Katalin Toth[2], Martin Beaulieu[1]

[1]University of Toronto, [2]Université Laval, [3]New York University, [4]Université de Montréal

The Fragile X Related Protein 1 (Fxr1) is an RNA binding protein involved in the regulation of protein synthesis. Recent studies in humans suggest that Fxr1 is a genetic risk factor for schizophrenia and may affect disease severity in bipolar disorder. Moreover, experiments on mice show that mood stabilizers affect Fxr1 expression. We modulated level of Fxr1 expression directly in the brain of adult mice or in primary cortical cultures to study its role in synaptic neurotransmission. Whole cell patch-clamp recordings of mPFC layer III-V pyramidal neurons revealed significant decrease in the sEPSC frequency and amplitude in neurons with Fxr1 overexpression. In addition, the rectification index of eEPSCs was significantly increased indicating prevalence of CP-AMPARs in these neurons. In vivo, homeostatic plasticity was induced using sleep deprivation, which resulted in the increase of mEPSCs amplitude and decrease of decay time constant, mediated by CP-AMPAR currents elevation. These homeostatic changes were abolished by Fxr1 overexpression and by knockdown of its negative regulator Gsk3b. Similarly, modulation of Fxr1/Gsk3 also prevented synaptic upscaling induced by TTX application in primary neuronal cultures. Thus, our data suggest involvement of Fxr1 in the regulation of AMPAR composition and alteration of synaptic strength during different forms of homeostatic synaptic plasticity. Therefore, this protein might be an efficient target not only for mood disorders treatment, but also other neurological diseases with destabilized homeostatic synaptic plasticity.

3-B-30 Differential expression of gangliosides across multiple microglial phenotypes and their role in fine-tuning microglia activation

Danny Galleguillos[1], Qian Wang[1], Karin Rubinstein[1], Matthew Churchward[2], Kamaldeep Dhami[1], Kathryn Todd[2], Simonetta Sipione[1]

[1]Neuroscience and Mental Health Institute - University of Alberta, [2]University of Alberta

Ganglioside are sialic acid-containing glycosphingolipids highly enriched in the CNS. They are crucial mediators of cell-to-cell communication and play important roles in cell signaling. Knockout of ganglioside biosynthetic enzymes in mouse models leads to neurodegeneration accompanied by increased number of microglia and up-regulation of pro-inflammatory cytokines. Most studies have focused on the role of gangliosides in neurons, but little is known about their functions in microglia. We investigated the expression of ganglioside biosynthetic enzymes as well as levels of gangliosides in microglia exposed to different polarizing conditions. Changes in the ganglioside profile and in the relative expression of ganglioside biosynthetic

enzymes were observed in each polarization state, suggesting a potential role of specific gangliosides in microglia functions. Modulation of gangliosides levels with a pharmacological agent resulted in significant alteration of microglia function and response to external stimuli, including changes in inflammatory responses, expression of growth factors and polarization markers. Microglial gangliosides levels were also found to affect phagocytic activity and chemotaxis. Altogether, our data indicates that gangliosides are important modulators of microglia functions and suggest that gangliosides could be exploited therapeutically in conditions with a neuroinflammatory component.

3-B-31 Non-uniform subthreshold dynamics and integrative features in dorsal raphe neurons

Emerson Harkin[1], Michael Lynn[2], Alexandre Payeur[1], Andre Longtin[2], Richard Naud[2], Jean-Claude Beique[3]

[1]University of Ottawa Brain and Mind Research Institute, Centre for Neural Dynamics, [2]University of Ottawa Brain and Mind Institute, Centre for Neural Dynamics, [3]University of Ottawa

The serotonin neurons of the dorsal raphe nucleus (DRN), which provide the majority of the forebrain's serotonergic input, play a particularly important role in regulating behavioural responses to emotionally-salient stimuli. The DRN receives numerous long-range parallel inputs and it is unclear how this network processes this complex information stream. A minimal understanding of the dynamical features of single neurons is a required prerequisite for the development of satisfactory network-level models of this important hub. To address this issue, we set out to develop an experimentally-constrained computational model of raphe neurons that accurately reproduces the electrophysiological responses of individual cells to a variety of complex inputs. We observed non-linear subthreshold dynamics in these neurons that could not be readily captured by a generalized leaky-integrate-and-fire model (GLIF) often used for network-level modelling. The addition of a minimal set of experimentally-derived conductances was necessary for satisfactory model performance. During the course of this work, we observed intriguing heterogeneity in the subthreshold nonlinearities of this population, and explore how these affect the integration features of defined synaptic inputs. This work raises the possibility of distinct integrative modules within the raphe network.

3-B-32 The glial source of TNF during homeostatic synaptic plasticity

Renu Heir[1], Pragya Komal[1], Marie Franquin[1], Julien Chambon[1], David Stellwagen[1]

[1]McGill University

For neural circuits to function well, overall activity levels must be kept within an optimal range by homeostatic synaptic plasticity (HSP) mechanisms. The process of homeostatic strengthening of excitatory synapses in response to chronic activity deprivation is mediated by the glial release of tumour necrosis factor alpha (TNF), which modulates both AMPA and GABA synaptic receptor trafficking. While it has become clear that glia play a critical role in some forms of HSP, the glial source--whether from astrocytes or microglia--has been a matter of some debate. Here we show that astrocytes supply TNF during HSP in dissociated cultures, and that this occurs at least in part through regulation of TNF mRNA levels. We show that 48 hour activity deprivation of cultures with tetrodotoxin (TTX) results in both an increase in TNF mRNA levels as well as an increase in surface GluA1 levels. Depletion of microglia from these cultures does not prevent TNF release in response to TTX, nor does it prevent the increase in surface GluA1, suggesting that astrocytes are producing TNF in this context. In addition, we use organotypic hippocampal slice cultures to investigate glial release of TNF in a situation more closely representing in vivo conditions. We find that in slice cultures where TNF is genetically deleted from microglia, mEPSC amplitude still increases in response to activity deprivation, suggesting that microglial TNF is not necessary for this effect. We therefore show that in multiple culture systems, astrocytes are capable of supplying the TNF that results in HSP.

3-B-33 Microglia-driven cognitive impairments in offspring of dams with gestational diabetes

Jin Hee Kim[1], Lori Tessler[1], Tiina Kauppinen[1]

[1]University of Manitoba

Gestational diabetes mellitus (GDM) is complication during pregnancy resulting elevated blood glucose and inflammation. Increasing evidence suggest that fetal GDM exposure causes cognitive impairments in offspring. We have established that PARP-1 has a key role in regulation of microglia, the resident brain immune cells. Here we hypothesized that microglial PARP-1 ablation reduces neuroinflammation-driven pathological changes in developing neuronal networks and rescues cognitive abilities of the offspring exposed to GDM. We studied 15-week old male offspring of diet-induced GDM dams and compared them to ones from dams with

healthy diet (Lean). The GDM exposure induced cognitive impairments associated with hippocampal reduced synaptic protein expression, structural changes in CA1 neuronal layer and neuroinflammation in wt offspring, but these GDM effects were reduced in offspring with microglia-targeted PARP-1 depletion. Microglia cultures prepared form GDM offspring showed hyper-sensitivity, which was abolished by PARP-1 deletion and inhibition. Furthermore, constitutive microglial PARP-1 activation driving prolonged microglial inflammatory responses in healthy mice led to similar cognitive and cellular changes as seen in GDM offspring. In combine our data suggests that GDM induces PARP-1-driven chronic microglial pro-inflammatory responses, which leads to hippocampal neuronal changes resulting in cognitive impairments in the offspring. Microglial modulation serves as a therapeutic opportunity to prevent behavior changes, and memory and learning impairments in GDM offspring

3-B-34 Quality control of hiPSCs-derived neurons and astrocytes: assessing and improving maturation

Mahshad Kolahdouzan[1], Marie Franquin[1], Blandine Ponroy[1], Huashan Peng[2], Carl Ernst[1], David Stellwagen[1]

[1]McGill University, [2]McGill

Human induced pluripotent stem cells (hiPSCs) can be obtained through reprogramming any cell type, by inducing the expression of 4 pluripotency genes. hiPSC-derived neurons and astrocytes have been proposed as models to study different neurodegenerative diseases, such as ALS. We aim to develop and characterize mature neurons and astrocytes from human induced pluripotent stem cells. For neuronal differentiation, we tested different combinations of growth factors and assessed neuronal maturation via calcium imaging, electrophysiology, mRNA levels of neuronal markers and immunocytochemistry. For astrocytes, we compared three different protocols; a) 2 months of astrocyte differentiation, b) 2 weeks of neurogenesis followed by 2 months of astrogenesis, and c) 3 weeks of neurogenesis followed by 2 months of astrogenesis. We then characterized the astrocytes through qPCR and immunocytochemistry for neuron progenitor cell (NPC) and astrocytic markers. We found that the 3rd protocol, which incorporated 3 weeks of neurogenesis and 2 months of astrogenesis, had lower mRNA levels of NPC markers vs. the first protocol, and higher mRNA levels of mature astrocyte markers compared to the other two protocols. Therefore, the neurons and astrocytes developed from these protocols may provide a non-invasive and useful tool to study neurodegenerative

diseases. We can use these cells to confirm findings in animal studies, and further investigate mechanisms underlying disease pathophysiology.

3-B-35 The neuron baseball card project: A catalog of interneuron types in the primate lateral pre-frontal cortex

Eric Kuebler[1], Megan Roussy[2], Jackson Blonde[1], Roberto Gulli[1], Rogelio Luna[1], Gustavo Parfitt[1], Jude Reslan[1], Michelle Jimenez[1], Julia Sunstrum[1], Sara Matovic[1], Meagan Wiederman[1], Chakravarthi Narla[1], Jaymin Jeong[1], Michelle Everest[1], Kim Thomaes[1], Rhonda

[1]Robarts Research Institute, [2]University of Western Ontario

For many years researchers have been interested in phenotyping neurons according to electrophysiological and morphological features. This has, up to now, been largely focused on neurons from rodents, with some recent emphasis on the characterization of human cells. However, to our knowledge, a library of the electrophysiological and morphological characteristics of interneurons in macaques is incomplete. The small amount of information that does exist indicates differences between rodents and monkeys for both functional properties of pyramidal neurons, and anatomical brain regions. Here, we employed in vitro patch clamp experiments to record from neurons of the lateral prefrontal cortex of two rhesus macaques. A total of 98 current clamp recordings were obtained from the two animals. Several characteristics of action potentials were measured, including: peak, half width, height, threshold, as well as the properties of spike trains, ie. firing rates. Based on these characteristics we have identified several different interneurons: fast and regular spiking, fast and slow accommodating, rebounding, adapting, etc. We have also reconstructed the morphologies of many of these neurons and have noted both similarities and differences between primate and rodent. However, some morphologies in primate have not been reported in rodent. Our long-term goal is to integrate these data in to the behaviour of circuits of the prefrontal cortex to better understand how different interneurons participate in network function. Our custom Matlab scripts will be available as open source software.

3-B-36 Rapid cAMP signalling regulates postsynaptic structural modification underlying synaptic plasticity

Tyler Luyben[1], Jelena Borovac[2], Megan Valencia[2], Fiona Bergin[3], Mustafa Khan[3], Hang Li[3], Takashi Tominaga[4], Kenichi Okamoto[5]

[1]Visa, [2]University of Toronto, [3]The Lunenfeld-Tanenbaum Research Institute, [4]Tokushima Bunri University, [5]Lunenfeld-Tanenbaum Research Institute

Understanding how synaptic structure and function are modulated by neuronal activity is essential for elucidating the mechanisms of learning/memory. Here we describe postsynaptic cAMP-dependent mechanisms to regulate structural synaptic plasticity which is crucial for activity-dependent maturation/refinement of neural circuits. NMDA receptor-dependent strong synaptic stimulation induces the activation of CaMKII that triggers long-term potentiation (LTP). The induction also leads to enlargement of postsynaptic structures (dendritic spines) in a process called structural long-term potentiation (sLTP). The postsynaptic cAMP pathway is thought to invoke a protein synthesis-dependent increase in synaptic strength. However, its role in the structural change of dendritic spines remains elusive. Using novel two-photon optogenetic approaches to directly increase or decrease cAMP levels by light at target dendritic spines, we identified and characterized a mechanism of postsynaptic cAMP that enhances sLTP using rodent hippocampal CA1 pyramidal neurons of organotypic cultured slices. The cAMP/PKA signal is required for structural remodeling independently of cAMP-mediated protein synthesis and also regulates sLTP by coupling with CaMKIIβ activity, which controls the actin cytoskeleton in dendritic spines. Furthermore, cAMP affects sLTP not only at activated spines but also in neighboring spines which are not directly activated, suggesting a local neural circuit level cAMP function. Thus, the cAMP mechanism could underlie synaptic interplay as a fundamental feature of learning and memo

3-B-37 Frequency coding at individual CA1 synapses

Cary Soares[1], Andre Longtin[1], Richard Naud[1], Jean-Claude Beique[2]

[1]University of Ottawa Brain and Mind Institute, Centre for Neural Dynamics, [2]University of Ottawa

Transmission at single synapses in the brain is stochastic, unreliable and variable. The impact of such synaptic noise on neural coding still remains incompletely understood. Here, we revisited and expanded upon key concepts of glutamate release at single dendritic spines of CA1 pyramidal neurons using whole-cell electrophysiology, two-photon glutamate uncaging and imaging of a genetically-encoded optical glutamate sensor. We provide an estimate of the variability in cleft glutamate concentration, and describe the ability of postsynaptic glutamate

receptors to transmit such variability. Both the amount and the variability of glutamate release is regulated by firing frequency. We developed a parsimonious model which captures these observations and highlight their computational roles. By showing frequency coding at single synapses, this work expands the classic view on the nature of information transfer at central synapses.

3-B-38 Ventral pallidum Drd3-expressing neurons mediate persistent cocaine seeking behaviors

Horia Pribiag[1], Sora Shin[1], Eric Wang[1], Varoth Lilascharoen[1], Byungkook Lim[1]

[1]University of California, San Diego

Addictive substances hijack the brain's reward system, generating a persistent drive for drug seeking at the expense of natural rewards. Although drug-induced plasticity in the striatum is known to play a critical role in addictive behaviors, persistent drug-induced alterations in other mesolimbic brain structures that integrate and convey reward-related information remain less understood. We found altered dopamine receptor D3 (Drd3) gene expression in the ventral pallidum (VP) in response to prolonged withdrawal from cocaine administration, suggesting that Drd3 signaling in the VP may participate in drug-induced plasticity in the VP. We explored the role of VP Drd3 signaling in plasticity and drug seeking following withdrawal from cocaine self-administration and uncovered significantly altered activity in VP Drd3+ neurons during drug seeking. Using viral-mediated tracing, electrophysiology and optogenetics we characterized VP Drd3+ projections to different brains areas, identifying roles for distinct projections in mediating reward-related behavior. Our results provide insight into the role of dopaminergic signaling in the VP and a mechanistic understanding of how VP Drd3-expressing neurons may be critical for driving persistent drug seeking behavior.

3-B-39 Aryl hydrocarbon receptor nuclear translocator-2 expression in glia is influenced by inflammatory mediators in vitro and in models of multiple sclerosis

Pierre Becquart[1], Jake Johnston[1], Maria-Elizabeth Baeva[1], Jacqueline Quandt[1]

[1]University of British Columbia

Multiple sclerosis (MS) is a chronic CNS inflammatory and neurodegenerative disorder. Aryl hydrocarbon receptor nuclear transporter-2 (ARNT2) is a key modulator of neuronal development and axonal health, partnering to drive transcription of growth factors including brain-derived neurotrophic factor (BDNF). We hypothesize ARNT2 influences glial function and trophic support in inflammatory settings. ARNT2 expression was characterized in experimental autoimmune encephalomyelitis (EAE, the animal model of MS) and in primary astrocyte-enriched cultures or oligodendrocyte precursor cells (OPC) exposed to stressors and inflammatory mediators. ARNT2 is expressed in astrocytes extending from the meninges and along the central canal of healthy spinal cords. In EAE, the frequency of astrocytes increases however the proportion of astrocytes expressing ARNT2 is half that observed in healthy mice. Lower ARNT2 corresponded with decreased levels of BDNF. In vitro, astrocytes constitutively express low levels of ARNT2. Both oxidative stress and serum deprivation increase ARNT2 expression by as much as 30%. Approximately 50% of Olig2+ cells in the healthy CNS express ARNT2 yet this is reduced by half at peak disease, most notably in the grey matter. OPC express moderate levels of ARNT2 which decrease following maturation with cAMP to drive myelin production. In this first description of glial ARNT2 expression, we show ARNT2 is associated with trophic support in disease settings. Characterization of glial-specific ARNT2 expression for its functional relevance to repair in MS is warranted.

3-B-40 Ethanol inhibition of long term depression and NMDA receptor currents in the developing rat dentate gyrus

Scott Sawchuk[1], Brian Christie[1]

[1]University of Victoria

Ethanol is believed to provide a direct block of N-methyl D-aspartate receptors (NMDAr) , and whole-cell patch clamp analysis has shown that ethanol can inhibit NMDAr currents in hippocampal CA1 and cortical pyramidal cells, as well as DG granule cells in vitro. Patch-Clamp analysis of NMDA receptor currents in cultured neurons have indicated that ethanol's effects on NMDArs are distinct for different NMDAr subunits (i.e. GluNR1, GluNR2(A-D) and GluNR3(A-B)). As drastic changes in the expression profile of NMDAr subunits occurs during development, this becomes an important consideration for studies involving ethanol's effects on NMDAr dependent synaptic plasticity throughout development. Here we describe ethanol inhibition (50 and 100mM) of NMDA receptors in the DG of the developing rat hippocampus using whole-cell patch clamp analysis at post-natal days 14, 21 and 28. We also examine how acute ethanol

exposure affects traditional long-term depression (1Hz x 900) at each of these timepoints. The goal of this work is to describe how a changing NMDAr subunit profile affects DG-LTD throughout development, as well as the sensitivity of DG-LTD and NMDAr currents in DG granule cells to ethanol throughout development.

3-B-41 Dense core vesicle transport and synaptic capture in neurons

Alexandra Vela[1], Michael Silverman[1]

[1]Simon Fraser University

Neurons are highly polarized and compartmentalized cells and rely on vesicle trafficking for proper development and function. Formation of presynaptic and postsynaptic sites depends on transport of dense core vesicles (DCVs) to these locations and relies on synaptic resupply after vesicle fusion. Moreover, reduced availability of DCV cargos, e.g., neurotrophins, contributes to neurodegenerative disorders, such as Parkinson's and Alzheimer's disease. Therefore, it is important to understand the mechanisms underlying the targeting and capture of DCVs. Here, we use live cell imaging and movement analysis of DCVs carrying fluorescently-tagged brain-derived neurotrophic factor (BDNF) in spontaneously active hippocampal neurons to assess transport behaviors as they translocate to presynaptic sites. Transport in axons was highly processive in both anterograde and retrograde directions and vesicles are capable of reversing direction mid-axon. Notably, when translocating to synaptic sites, DCVs can arrive from either direction. We then observed vesicle capture (stationary >5 min) at presynaptic sites, yet in most cases, vesicles pause temporarily and then resume movement. These results indicate that motor proteins of both polarities, i.e., kinesin and dynein are capable of DCV delivery to synapses. Studies are underway to identify signaling cascades that regulate these transport processes to ensure efficient DCV capture.

3-B-42 Quantifying dendritic chloride dynamics in cytotoxic edema using fluorescence lifetime imaging

Nicholas Weilinger[1], Brian MacVicar[2]

[1]Centre For Brain Health / University of British Columbia, [2]University of British Columbia

Chloride (Cl-) flux controls cell volume by altering cytosolic tonicity. As such, Cl- gradients across the neuronal plasmalemma are tightly constrained to defend cell volume, rendering it difficult to experimentally control intracellular Cl- concentration ([Cl-]i) by whole-cell patch clamp. We are using fluorescent lifetime imaging (FLIM) to quantify [Cl-]i in whole cell recordings to investigate intrinsic variability in Cl- handling between and within cells. We asked how the subcellular [Cl-]i distribution was influenced by excitatory activity to glean insights into Cl- influx and cellular swelling (cytotoxic edema). Layer 4 pyramidal neurons were whole-cell patch-filled with the Cl-sensitive dye MQAE, enabling us to map shifts in [Cl-]i and commensurate changes in volume of dendritic shafts and spines. Patched neurons maintained dendritic (but not somatic) [Cl-]i at baseline levels by homeostatic function of the K+/Cl- cotransporter (KCC2) despite dialysis of the recording solution. Depolarization increased [Cl-]i and was exacerbated by blocking KCC2 with furosemide. In contrast to depolarization alone, NMDA-triggered excitotoxicity elicited massive Cl- entry upwards of 70mM from rest (~10mM) and dendritic beading. Under these conditions, localized [Cl-]i heterogeneities were observed along dendritic shafts/spines, with severe beading occurring in regions where [Cl-]i was highest. We conclude that dendritic [Cl-]i is stabilized at rest in patched neurons and is overwhelmed by NMDA activation, revealing distinct Cl- microdomains that couple directly to membrane beading.

3-B-43 Pannexin-1 dependent long-term depression at the CA3-CA1 synapse

Allison Werner[1], Roger Thompson[1]

[1]University of Calgary

Long-term depression (LTD), a form of synaptic plasticity characterized as a long-lasting decrease in synaptic strength, may be critical for learning and memory. Postsynaptic NMDA receptor-dependent LTD (NMDAR-LTD) is a classical form that requires calcium influx through NMDARs to activate a protein phosphatase cascade and decrease postsynaptic AMPA receptors. However, aspects of this model have recently been challenged. Rather than ion influx through the NMDAR, LTD may instead require metabotropic signalling by the NMDAR. We recently reported that Pannexin-1 (Panx1) channels are regulated by metabotropic NMDAR activity during excitotoxicity via recruitment of Src family kinases (SFKs). Thus, we hypothesized that a Panx1-dependent form of LTD involves metabotropic NMDAR signalling. Using whole cell patch clamp electrophysiology, we recorded LTD in CA1 pyramidal neurons following low-frequency stimulation (LFS; 3Hz, 900 pulses) to the Schaffer collaterals. Inhibition of NMDAR metabotropic signalling with the competitive antagonist, APV prevented LTD induction, whereas application of

the pore-blocker, MK-801 did not. Panx1 block or an SFK inhibitor (PP2) prevented LTD induction. Together this suggests NMDAR-LTD may require metabotropic signalling by the NMDAR through SFKs leading to the activation of Panx1.

3-B-44 Antibiotic treatment disrupts synaptic plasticity in the PVN and impairs memory of an acute stress

Agnieszka Zurek[1], Toni-Lee Sterley[1], Dina Baimoukhametova[1], Jaideep Bains[2]

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

Perturbation of the gut microbiome can alter the hormonal and behavioral response to acute stress. The neural changes associated with an altered stress response after antibiotic treatment are unknown. Here we investigated whether a short, 1 week course of antibiotics altered neuronal function in the paraventricular nucleus (PVN) of the hypothalamus, which integrates information regarding physiological and psychological stressors and initiates the stress response. We show that one week of antibiotic treatment is sufficient to decrease bacterial load and alter gut microbial composition at the phylum level. The treatment has no effect on basal neuronal firing, synaptic glutamate and GABA transmission or basal levels of the stress hormone, corticosterone. In response to footshock, antibiotic-treated mice show increased levels of corticosterone (compared to water-treated controls), a deficit in stress-induced plasticity at glutamate synapses in the PVN and impaired memory of a stressful experiences. These results suggest that antibiotic treatment disrupts the normal behavioural and neural response to stress.

3-C-45 18F-FDG PET imaging of brain glucose hypometabolism in the 3xTg mouse model of Alzheimer's disease

Aida Adlimoghaddam[1], Wanda Snow[1], George Stortz[2], Andrew Goertzen[3], Ji Ko[3], Jelena Djordjevic[4], Claudia Perez[4], Benedict Albensi[1]

[1]St. Boniface Hospital Research Centre / University of Manitoba, [2]niversity of British Columbia, [3]University of Manitoba, [4]St. Boniface Hospital Research Centre

Alzheimer's disease (AD) is a progressive age-related neurodegenerative disease. Although neurofibrillary tangles (NFTs) and amyloid beta (AB) are common hallmarks of AD, the earliest deficits in the pathological progression of AD seem to be caused by impaired brain metabolism.

Therefore, efforts to detect alterations in brain metabolism could improve our ability to diagnose AD in early stages and identify more effective treatment targets. The current study utilized FDG-PET to measure abnormalities in brain metabolic activity in AD mice and control mice. Both 3xTg-AD mice and control mice underwent FDG-PET neuroimaging. Further, congo red staining and immunohistochemistry were utilized to detect neuropathology of Aβ and NFTs. Moreover, we measured the activity of mitochondrial enzymes involved in the metabolic pathways. Western blotting was used to determine protein levels of Complex I-V subunits. We found significant brain hypometabolic changes ($p < 0.05$) as measured by FDG-PET in cortical insular and piriform regions of AD brains compared to that of control brains. Also, we found a significant reduction ($p < 0.05$) in the activity of mitochondrial cytochrome c oxidase as well as significant decreases ($p < 0.05$) in expression of mitochondrial complex protein subunits in AD brain as compared to control brains. No significant differences were found in the activity of citrate synthase or GAPDH between AD and controls. No congophilic positive Aβ was detected in any brain region in either AD/control mice; however, we detected NFTs in the entorhinal cortex, parasubiculum, and

3-C-46 SMaRT Human Neural Stem Cells to Degrade Glial Scar and Enhance Regeneration after Cervical Spinal Cord Injury

Christopher Ahuja[1], Mohamad Khazaei[1], Jian Wang[1], Michael Fehlings[2]

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

Human induced pluripotent stem cell-derived neural stem cells (hiPS-NSCs) represent an exciting therapeutic strategy to regenerate after spinal cord injury (SCI). Unfortunately, most patients are the in chronic injury phase where a dense perilesional chondroitin sulfate proteoglycan (CSPG) scar hinders neurite outgrowth and cell migration. CSPG-degrading enzymes can enhance NSC-mediated recovery, however, nonspecific intrathecal administration leads to off-target effects. We aimed to genetically engineer hiPS-NSCs to express a scar-degrading enzyme into their local environment to enhance functional recovery after SCI. A scar-degrading enzyme was non-virally transfected into hiPS-NSCs; the resultant SMaRT cells stably express the enzyme which rapidly degrades human CSPGs in vitro and allows neurons to extend into scar-like CSPG-rich regions. Conditioned SMaRT cell media also degrades rodent CSPGs in ex vivo injured cord sections. T-cell deficient rats (N=60) with chronic C6-7 SCIs were randomized to (1) SMaRT cells, (2) hiPS-NSCs, (3) vehicle, or (4) sham surgery. While a battery of blinded in vivo neurobehavioural assessment are being analyzed to 40 weeks, interim

histological analyses show grafted human cells extending remarkably long (≥20,000μm) axons along host white matter tracts. This work provides exciting proof-of-concept data that genetically-engineered SMaRT cells can degrade CSPGs in vitro and that human NSC transplants can generate long axons in chronic cervical SCI.

3-C-47 Neuregulin-1: a novel regulator of immune response in traumatic spinal cord injury

Arsalan Alizadeh[1], Kallivalappil Santhosh[1], Hardeep Kataria[1], Adelilah S. Gounni[1], Soheila Karimi-Abdolrezaee[1]

[1]University of Manitoba

Spinal cord injury (SCI) triggers a robust neuroinflammatory response with both degenerative and pro-regenerative effects. Promoting the supportive aspect of immune response is a viable approach for the treatment of SCI. We previously demonstrated that SCI results in an acute and permanent depletion of the neuronally derived Neuregulin-1 (Nrg-1) in the spinal cord. Increasing the dysregulated level of Nrg-1 through acute Nrg-1 treatment enhanced endogenous cell replacement and promoted white matter preservation and functional recovery in a clinically-relevant model of moderately severe compressive SCI in rats. Here, we elucidated the effect of systemic Nrg-1 therapy on the recruitment and function of macrophages, T and B cells following SCI. We conducted flow cytometry, qPCR and immunohistochemistry to study systemic and spinal cord immune response as well as cytokine, chemokine and antibody production. We provide novel evidence that Nrg-1 promotes a pro-regenerative regulatory phenotype in T and B cells and macrophages in the spinal cord and blood during the acute and chronic stages of SCI. Importantly, Nrg-1 fostered a more balanced post-SCI microenvironment by attenuating antibody deposition and expression of pro-inflammatory cytokines and chemokines while upregulating pro-regenerative mediators. Our work establishes the promise of Nrg-1 treatment as a candidate immunotherapy for traumatic SCI and other CNS neuroinflammatory conditions.

3-C-48 Stress controllability reverses chronic stress-induced behavioural deficits: involvement of cortical endocannabinoids

Courtney Leigh Clarke[1], Victoria Elizabeth Mackey[1], Jordan Osmond[1], Sarah Bugden[1], Francis Bambico[1]

[1]Memorial University of Newfoundland

Depressive disorders can arise from a perceived lack of control over stressors, a phenomenon that is linked to perturbed prefronto-raphe neurotransmission. Cognitive-behavioural and remediation therapies ameliorate mood-related symptoms by enhancing perceived controllability overs stressors. We developed a rodent model of cognitive remediation based on a modified Morris water maze (with vs. without an escape platform) in mice. Animals were first exposed to at least 6 weeks of chronic unpredictable stress (CUS), then were submitted to behavioural control training (BCT), where BCT+ animals were repeatedly allowed to learn to evade the stressors, while BCT- were subjected to inescapable stressors. CUS-exposed animals exhibited depressive-like (sucrose consumption, fruit loops and forced swim tests) and anxiety-like reactivity (novelty-suppressed feeding and elevated plus maze), and increased serum corticosterone levels. These behavioural deficits were reversed by 8-10 days but not by 3 days of BCT in CUS-exposed BCT+ animals and not in CUS-exposed BCT- animals. The therapeutic-like effects of BCT was nullified by administration of the cannabinoid CB1 receptor antagonist AM251 and recapitulated by the endocannabinoid enhancer URB597. We are currently assessing changes in the PFC by electrophysiological recordings of PFC and raphe neuronal activity after CUS and BCT (BCT+ vs. BCT-), as well as CUS and BCT-induced changes in CB1 receptors density and fatty acid amide hydrolase (FAAH) expression.

3-C-49 Development of an opioid self-administration assay to study drug seeking in zebrafish

Gabriel Bosse[1], Randall Peterson[1]

[1]University of Utah

Drug addiction is a state defined by compulsive engagement in naturally rewarding behavior or drug use, despite adverse consequences. The zebrafish (Danio rerio) has become an excellent tool to study mental health disorders. Zebrafish have been shown to exhibit characteristics of addiction to drugs of abuse in non-contingent assays, including conditioned place preference. However, thus far, a single contingent assay has been reported for alcohol consumption. Using inexpensive electronic, mechanical, and optical components, we developed an automated opioid self-administration assay for zebrafish to measure drug seeking and gain insight into the

underlying biological pathways. Zebrafish trained in the assay for five days exhibit robust self-administration. In addition, as with other animal models, conditioned fish continue to seek the drug despite an adverse consequence and can be tested under a progressive ratio. Furthermore, fish trained in our assay also showed signs of stress and anxiety upon withdrawal of the drug. Finally, we validated our assay by confirming that self-administration in zebrafish is dependent on several of the same molecular pathways as other animal models. Given the ease and throughput of this assay, we are currently performing a small molecule screen to identify new factors regulating drug seeking. This screen will enable the identification of important biological pathways regulating drug seeking and could lead to the development of new therapeutic molecules to treat addiction.

3-C-50 Impact of minocycline treatment on spatial learning and memory performance following prenatal alcohol exposure

Melissa Chiu[1], Amanada Chao[1], Srishti Sarkar[1], Samantha Baglot[1], Tamara Bodnar[1], Joanne Weinberg[1]

[1]University of British Columbia

Prenatal alcohol exposure (PAE) can lead to learning deficits, endocrine imbalances and behavioural impairments. Both clinical studies and animal models have consistently uncovered immune system deficits following PAE. PAE has been shown to impact the neuroimmune system by activating microglia and altering cytokine release, which can affect cognition and spatial learning/memory. Using a PAE animal model, we tested whether minocycline, a microglia-targeting antibiotic, could dampen the neuroimmune system to improve spatial learning/memory. Pregnant Sprague-Dawley rats were assigned to either: PAE (liquid ethanol diet) or control (control diet) groups. Offspring were given minocycline during lactation or adolescence, or were left untreated. In adulthood, offspring were tested in the Barnes Maze to assess spatial learning/memory. Preliminary data showed baseline spatial learning/memory deficits following PAE. Specifically, the distance travelled in the incorrect zone of the Barnes Maze by untreated PAE male rats was greater than that of control male rats, indicating that PAE male rats utilized a less efficient strategy to find the target zone. However, administration of minocycline appeared to normalize the search strategy of PAE rats, as demonstrated by decreased time spent in the incorrect zone compared to control rats. This suggests that minocycline may play a role in improving spatial learning/memory performance following PAE.

Further research is needed to evaluate the mechanistic involvement of the neuroimmune system. Support: NIH/NIAAA RO1 AA022460, R37 AA007789

3-C-51 Post-mortem analysis of a Parkinson's disease brain after 11 years of deep brain stimulation of the subthalamic nucleus

Francis Desmeules[1], Cynthia Lecours[2], Sylvine Carrondo Cottin[3], Angela Noecker[4], Peter Gould[3], Stephan Saikali[3], Marie-Eve Tremblay[2], Cameron McIntyre[4], Michel Prud'Homme[3], Léo Cantin[3], Martin Parent[5]

[1]CERVO Brain Research Centre, [2]Centre de recherche du CHU de Québec, [3]Hôpital de l'Enfant-Jésus, [4]Cleveland Clinic, [5]Université Laval

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is now widely used to treat Parkinson's disease (PD). Even if this procedure does not cure the disease, it radically alleviates motor symptoms, improves quality of life and allows reduction of dopamine medication and severe associated adverse events such as dyskinesia. The mechanisms of DBS as well as its long-term effects on cerebral tissue are poorly understood. This case report includes a detailed histopathological description of a PD patient's brain treated with DBS during 11 years, the longest STN stimulation period ever reported. Clinical data indicates positive outcomes of DBS on physical functioning with a score going from 48 to 11 on UPDRS III. We also noted a daily reduction of dopamine medication by 70% following DBS. Post-mortem 3D reconstructions indicate that active contacts were placed in the dorsolateral part of the STN, corresponding to the sensorimotor area. This 3D virtual environment was then used to model current spreading throughout the tissue. As expected, we observed a 300µm width gliosis around the electrodes. We also identified highly varicose GFAP+ astrocytes strongly expressing PCNA, exclusively in STN stimulated areas. Furthermore, significant reduction of the number of Iba-1+ microglia was observed along with reorientation of SERT+ axons in the stimulated STN areas, compared to non-stimulated STN regions. This study will help provide a better understanding of the long-term effects of chronic electrical stimulation and improve our understanding of DBS mechanisms of action.

3-C-52 Long-term 'fear-network' hyperconnectivity underlying threat perception in post-traumatic stress disorder

Benjamin Dunkley[1], Simeon Wong[1], Jimmy Wong[1], Margot Taylor[1]

[1]Hospital for Sick Children

Post-traumatic stress disorder (PTSD) is associated with heightened responses to threat in the 'fear circuit', and this is the primary driver of maladaptive hypervigilance. Previously we observed elevated synchrony in this network for soldiers with PTSD during an implicit emotion processing task captured at a single time point - the stability over time of this response has not been determined. We studied emotional face processing in soldiers with and without PTSD at two time points using MEG. At Time 1, 20 soldiers with and 25 without PTSD were scanned; 35 returned at Time 2, 2 years later, 13 with and 22 without PTSD. We computed phase synchrony as a measure of connectivity, and used a mixed effects model (group x time point). There were no significant differences in PTSD severity for T1 vs T2. MEG contrasts for angry faces revealed elevated connectivity in PTSD compared to controls - no significant differences were observed when contrasting T1 vs T2. This hypersynchrony in PTSD for threat was seen in subcortical regions, including the thalamus, and the ventromedial prefrontal cortex, cingulum gyri, inferior temporal and parietal regions. No significant differences were observed for either time or group in the happy condition. These results are consistent with our prior studies, and support the theory that hypervigilance in PTSD is driven by biased processing of threat, driven by a hypersynchronised 'fear network'. In conclusion, this effect was stable over time, in line with PTSD severity - therefore, these measures might constitute a reliable biomarker of the disorder.

3-C-53 Sensory-evoked activity in whisker barrel cortex as a model to probe cortical plasticity in a mouse model of Rett syndrome

Farnoosh Farhoomand[1], Jay Leung[1], Kerry Delaney[1]

[1]University of Victoria

Rett syndrome is a neurodevelopmental disorder occurring in about 1 in 10,000 live births due to loss of function of the X-linked transcription factor MeCP2. Symptoms usually begin to appear 6-18 months after birth and can include loss of speech, seizures, autistic features, and mental retardation. Here, we evaluate activity dependent plasticity in barrel cortex of symptomatic male Rett model mice, which lack MeCP2 (Mecp2tm1.1Jae), to better understand the consequences of MeCP2 loss-of-function for neural circuit performance. Primary somatosensory cortical response to whisker stimulation (20Hz-1sec) was assessed by intrinsic optical imaging. To induce cortical plasticity, C1 whisker was trimmed to 3 mm, and B2 was an

untrimmed control. We hypothesized that the normal reduction in cortical activity produced by deprivation would be attenuated in null vs. age-matched wild type (WT). The neuronal response to B2 wiggling was consistent from day 0 to 14 but reduced for C1 by 39.8 ± 5.5% in WT (n=10; $p<0.05$) and 14.8 ± 5.9% in Rett mice (n = 6; $p<0.05$). Normally sustained wiggling of untrimmed whiskers leads to a short-term reduction (habituation) in cortical response. The response to a long period of wiggling was 27.2 ± 4.9% smaller compared to a short period in WT (n=6), but only 12.8± 4.0% smaller in Rett mice (n=6) suggesting a reduced habituation response to repeated stimulation with loss of MeCP2 ($p<0.05$). Further studies will examine cortical responses and their activity dependent plasticity in presymptomatic male and pre-vs. post-symptomatic female Mecp2+/- mice.

3-C-54 Alterations of mismatch negativity (mmn) in schizophrenia patients differing on perceived spatial location of auditory hallucinations

Derek Fisher[1], Dylan Smith[2], Alain Labelle[3], Verner Knott[3]

[1]Mount Saint Vincent University, [2]University of Ottawa, [3]The Royal's Institute of Mental Health Research

Auditory verbal hallucinations (AHs), or hearing 'voices', are one of the hallmark symptoms of patients with schizophrenia (SZ). The primary objective of this study was to examine whether SZs with differing perceived locations of AHs also differ in the processing of auditory deviance, as indexed by the auditory mismatch negativity (MMN). MMNs to duration, frequency, gap, intensity and location were recorded in 21 SZ patients with persistent AHs and 15 healthy controls (HC). Patients were divided into those who experienced AHs as being inside the head only (SZI) and those with AHs outside the head (SZO). MMN amplitudes and latencies for each deviant were compared between groups. SZOs were found to have reduced right frontal location-MMN amplitudes compared to SZIs and HCs. Overall, we report differences in auditory change detection between schizophrenia patient groups that differ in the perceived location of auditory hallucinations. Whether these differences are due to structural abnormalities and/or functional differences between the groups remains unanswered.

3-C-55 Synaptic changes in the ALS cortex: an interplay between neurons and astrocytes

Marie Franquin[1], Mahshad Kolahdouzan[1], Blandine Ponroy[1], Pragya Komal[1], Carl Ernst[1], David Stellwagen[1]

[1]McGill University

Patients with amyotrophic lateral sclerosis (ALS) display cortical hyperexcitability and the most commonly used mouse model of ALS (SOD1G93A) shows similar cortical alterations, including hyperexcitability and increased miniature excitatory post-synaptic current (mEPSC) frequency at the pre-symptomatic stage of the disease in the layer V of primary motor cortex (M1). This could be driven by changes in astrocyte function, as neuronal-only expression of mutant SOD1 does not lead to an ALS phenotype and reactive astrocytes have been observed in patients with ALS. Reactive astrocytes would produce inflammatory signaling, which could trigger changes in homeostatic synaptic plasticity and lead to perturbed E/I balance in the cortical cells and hyperexcitability. We are studying this possibility in two models of ALS: the SOD1G93A mouse model and a human model based on the differentiation of human induced pluripotent stem cells (hiPSCs) from ALS patients into neurons and astrocytes. We are performing electrophysiological as well as morphological analysis in layer V pyramidal neurons of M1 in the SOD1G93A mouse model to determine the contribution of inflammatory signaling to the changes in synapses. We are also investigating changes in ALS versus control hiPSCs-derived astrocytes and neurons in order to determine if the disease could originate in altered interactions between those cell types, in particular through tumor necrosis factor alpha (TNF) signalling. Overall, this work will provide new insights into the cortical aspects of ALS and the implications of the different

3-C-56 Characterization of Adult Human Spinal Cord Stem Cell Proliferation/Differentiation Behavior: A Translational Perspective

Ahmad Galuta[1], Diana Ghinda[2], Mahmoud Bedaiwy[2], Hussam Jabri[2], Mohammad AlShardan[2], Michael Taccone[2], Carolyn Lai[2], Jessica Rabski[2], Suzan Chen[3], Eve Tsai[4]

[1]University of Ottawa, [2]Division of Neurosurgery, Department of Surgery / The Ottawa Hospital, [3]Ottawa Hospital Research Institute, [4]The Ottawa Hospital

Objective: Many spinal cord (SC) repair strategies in rodents have included the use of neural stem/progenitor cells (NSPCs). This study will compare the in vitro proliferation and differentiation characteristics of adult human and rat SC NSPCs. Methods: Adult human (n=13) and rat (n=10) SC NSPCs were cultured using the neurosphere assay and assessed for their

intrinsic behavior in 1%FBS. Alternatively, NSPCs were directed to differentiate by treatment with exogenous factors: RA, BMP4, or PDGFα and induced to proliferate with mitogens: EGF and FGF. NSPCs were treated for 7 and 14 days, and had BrdU administrated within the last 24 hours to track proliferation. NSPCs were then fixed and characterized using immunocytochemistry. Results: Human (n=4) and rat (n=5) NSPC differentiation profiles differ. Whereas human NSPCs formed more β-iii tubulin+ neurons (72.5±19.2%), rat NSPCs formed more GFAP+ astrocytes (63.8±8.6%). This was not due to differences in proliferation or cell death. Exogenous factor stimulation with RA induced neuron differentiation of human and rat NSPCs, BMP4 increased astrocyte differentiation of human NSPCs only, and PDGFα increased O4+ oligodendrocyte differentiation of rat NSPCs only. When stimulated with mitogens, Sox2+ NSPCs of humans and rats increased proliferation 3.7±0.7 fold and 5.5±0.4 fold, respectively, after a 14 day treatment. Conclusion: NSPC intrinsic behavior and response to the environment differs between humans and rats. This information is important to successfully translate therapeutic strategies based on animal NSPC studies to humans.

3-C-57 Investigating the early decline of neural stem cells in a mouse model of Alzheimer's disease

Richard Harris[1], Bensun Fong[1], David Park[1], Ruth Slack[1]

[1]University of Ottawa

Neurogenesis is the generation of new neurons from a pool of neural stem cells (NSCs) that occurs in discrete areas of the human brain including the subgranular zone of the dentate gyrus, a region responsible for cognition and memory. Yet, a decline in neurogenesis occurs with advanced age and has been implicated in memory impairments associated with Alzheimer's disease (AD). Our goal is to characterize the mechanism of NSC depletion in AD. 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 as early as 1 month of age. Anatomical measurements revealed a decrease in volume of the dentate gyrus by 1 month of age 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. Isolation of CD15-positive NSCs and subsequent RNA-seq analysis will reveal gene-regulatory pathways that contribute to NSC depletion. Lineage tracing analysis using an

inducible Nestin-driven Cre recombinase and a floxed-YFP reporter will identify defects in NSC self-renewal and maturation. These results will 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.

3-C-58 Effects of the type 1 cannabinoid receptor positive allosteric modulator GAT211 on absence seizures and the anxiety-like phenotype of Genetic Absence Epilepsy Rats from Strasbourg

John Howland[1], Quentin Greba[1], Mariam Alaverdashvili[1], Michael Anderson[1], Andrew Roebuck[1], Wendie Marks[1], Pushkar Kulkarni[2], Terrance Snutch[3], Ganesh Thakur[2], Robert Laprairie[1]

[1]University of Saskatchewan, [2]Northeastern University, [3]University of British Columbia

Genetic Absence Epilepsy Rats from Strasbourg (GAERS) are a rodent model of childhood absence epilepsy that display frequent absence seizures, and an anxiety-like phenotype in the elevated plus maze and increased acoustic startle. The present experiment tested the effects of acute treatment with the type 1 cannabinoid receptor (CB1R) positive allosteric modulator GAT211 (10 mg/kg) on absence seizures, and the anxiety-like phenotype of GAERS and a non-epileptic control (NEC) strain. In the first experiment, adult male GAERS were implanted with recording electrodes in sensorimotor cortex and hippocampus. After recovery from surgery, rats were well-habituated to a recording chamber and EEG was recorded twice for 3 h on separate days. Rats were treated (i.p.) with either vehicle (1:1:18 ethanol:emulphor:saline) or GAT211 (10 mg/kg) 1 h after recording was initiated. Initial analyses revealed that GAT211 decreased the total duration of seizures for 1 h after treatment. In the second experiment, male and female GAERS and NEC were treated with either vehicle or GAT211 (10 mg/kg) and then tested on tests of anxiety-like behaviour and locomotor activity including the elevated plus maze and acoustic startle. Vehicle-treated GAERS showed decreased open arm time on the elevated plus maze and increased startle when compared to NEC. Importantly, GAT211 treatment normalized both behaviours in GAERS without significant effects in NEC. These results suggest that positive allosteric modulation of CB1R may be effective for ameliorating absence seizures and their comorbidities such as anxiety.

3-C-59 Traffic Noise Stress Negatively Modifies Brain Structure-Function

Zahra Jafari[1], Bryan Kolb[1], Majid Mohajerani[1]

[1]University of Lethbridge

Road traffic is the main source of noise in the built-up environment of the city that engenders physiological reactions typical to those of stress. In addition to the deleterious impact of the daytime noise on well-being, chronic nocturnal noise can also disturb sleep and affects physical and mental health that has not been explored in rodents yet. This study was novel for investigating the impacts of chronic traffic noise exposure on mouse brain structure-function by considering the effects of light/dark cycles and sex. The mice were randomly assigned to either one of two stress conditions or a control condition. Animals were exposed to traffic noise on either the light-cycle (LC) or dark-cycle (DC) for 30 days. In this mouse model of traffic noise exposure, the HPA axis hyperactivity, anxiety-like behavior, deficits in learning and memory, impaired performance in balance and motor coordination, and a reduction in brain volume, medial prefrontal cortex (mPFC) area, cortical thickness, hippocampal volume, amygdala area, and the neural density in mPFC and dentate gyrus were deleterious effects of the chronic noise stress irrespective of the LC/DC exposure or sex. Our findings were a re-emphasis on the significance of noise prevention and mitigation strategies for public health.

3-C-60 Increased risk for heterotopic ossification and delayed bone consolidation in orthopedic patients suffering from a concomitant mild traumatic brain injury

Marianne Jodoin[1], Dominique Rouleau[2], Benoit Benoit[2], Stephane Leduc[2], Yves Laflamme[2], Emilie Sandman[2], Erik Therrien[2], Louis De Beaumont[1]

[1]Université de Montréal, [2]Sacred Heart Hospital of Montreal

Heterotopic ossification (HO) is an abnormal bone formation occurring in extra-skeletal tissues and is a common complication after an isolated limb fracture (ILF). Moderate/severe traumatic brain injuries (TBI) put orthopedic patients at risk for HO. Mild TBI is common in ILF patients but its impact on HO and delayed bone consolidation (BC), a common complication after an ILF, has never been explored before. This study aims to assess the risk for developing HO and delayed BC in mTBI+ILF patients. Methods: Patients with ILF were recruited from a Level 1 Trauma Center. Demographic information was gathered through a standardized questionnaire. All patients conducted an X-ray at 3 months post-trauma to assess signs of HO and delayed BC. Results: A total of 200 consecutive ILF patients were recruited (age: 48.54 years old; 111 women). Among them, 55 had also a mTBI. Results show that mTBI+ILF patients are significantly more at

risk of HO compared to ILF patients (X2= 10.78; p<0.01). Age, sex, and surgical procedures were not associated with HO. Delays in BC were significantly more present in mTBI+ILF patients (X2=14.94; p<0.01). Interestingly, results show an interaction between HO and BC in mTBI+ILF patients (X2=5.35; p=0.02) but not in ILF patients (X2=0.35; p=0.37). Conclusions: Results highlight substantial consequences of mTBI on fracture healing. The presence of mTBI in ILF patients should be considered as an indicator of high-risk of developing HO and delayed BC. Future studies should investigate possible pathophysiological mechanisms to help guide treatment protocols.

3-C-61 Mechanisms of AMPA-receptor trafficking alterations in a novel VPS35 p.D620N knock-in mouse model of Parkinson?s disease.

Chelsie Kadgien[1], Matthew Farrer[2], Austen Milnerwood[3]

[1]University of British Columbia | McGill, [2]University of British Columbia, [3]Montreal Neurological Institute

The pathogenic D620N (DN) mutation in vacuolar protein sorting 35 (VPS35) is linked to late-onset, autosomal-dominant Parkinson's disease (PD). VPS35 is a core component of the retromer complex, involved in endosomal recycling and intracellular trafficking of multiple neurotransmitter receptors. Here we explore retromer localization, binding of known interactors & novel cargoes, AMPAR, and early synaptic dysfunction in a novel D620N knock-in mouse model of PD. Western blot and immunoprecipitation were performed in tissue from wild-type and mutant mice to explore binding of receptors and known VPS35 interactors (including FAM21 - a member of the WASH complex which creates actin patches required for trafficking of retromer cargoes). In cultured cortical neurons, immunocytochemistry was used to explore survival and morphology, VPS35 cluster density, localization to endosomes, and colocalization with interactors. Fluorescence recovery after photobleaching was used to assay AMPAR surface recycling. Whole-cell patch clamp and immunocytochemistry were used to explore differences in synapse number and mini-excitatory post-synaptic current amplitude and frequency. Here we conclude that the D620N mutation alters FAM21 binding in tissue, glutamatergic synapse maintenance in cultured cortical cells from VPS35 D620N knock-in mice. Many genes linked to PD appear are involved in synaptic transmission; thus, understanding the role of VPS35 is important for uncovering how disruptions of neurotransmission lead to neurodegeneration in PD.

3-C-62 Adult-Generated GABA-ergic Neurons within the Injured Cortex after Stroke

Timal Kannangara[1], Anthony Carter[1], Jean-Claude Beique[1], Diane Lagace[1]

[1]University of Ottawa

Ischemic stroke promotes the proliferation and ectopic migration of precursor cells to damaged cortical regions. The impact of these cells to stroke recovery is unknown, as it is unclear whether any of these cells can functionally integrate into the spared cortical network. Here, we use a combination of whole-cell electrophysiology, immunohistochemistry and transgenic reporter strategies to identify and characterize the dynamic multilineage cellular response within the regions neighboring the stroke-injured, sensorimotor cortex. We find a population of adult-generated GABA-ergic cells that express immature neuronal markers, exhibit voltage-dependent conductances, fire action potentials, and receive GABAergic synaptic input. These findings show that adult-generated neurons have the capacity to integrate into the damaged sensorimotor cortex following stroke, which may permit their functional participation in stroke recovery.

3-C-63 The role of LRRK2 at cortico- and thalamo-striatal synapses

Naila Kuhlmann[1], Liping Cao[2], Matthew Farrer[1], Austen Milnerwood[3]

[1]University of British Columbia, [2]Centre for Applied Neurogenetics, [3]Montreal Neurological Institute

Altered striatal plasticity is implicated in numerous psychiatric and neurodegenerative disorders including Parkinson's disease (PD). While mutations in the PD-linked LRRK2 gene perturb several cellular functions, the effects on striatal plasticity are unknown. We previously reported that the LRRK2-G2019S mutation increases glutamatergic transmission in cultured cortical neurons and striatal slices from young G2019S knock-in (GKI) mice, suggesting a role in early pathophysiology. Here, we examined how these changes affect the cortico-striatal synapse, by measuring synaptic protein expression and miniature excitatory post-synaptic currents (mEPSCs) in co-cultured cortical and striatal spiny projection neurons (SPNs). Interestingly, GKI cortical neurons showed a distinct phenotype from those grown in monoculture: mEPSCs were similar to wild-type (WT) neurons, but both cortical and striatal neurons showed changes in VGluT1 and PSD95 clusters, indicative of altered synapse density. Furthermore, chemical manipulations of AMPAR, NMDAR and mGluR activity induced rapid and differential changes to synaptic protein levels in WT and GKI SPNs. Thus, LRRK2-G2019S alters synaptic organization and plasticity in

cortico-striatal co-cultures. We are now using selective optogenetic activation of thalamic and cortical inputs in GKI striatal slices to parse out input-specific effects, and how these may alter striatal plasticity. Given the striatum's role as gateway to the basal ganglia, identifying how PD-linked mutations shape striatal synapses may give clues to the early PD pathophysiology.

3-C-64 Expression of microRNA-21 in non-traumatic spinal cord injury is associated with poor motor function

Alex Laliberte[1], Spyridon Karadimas[1], Pia Vidal[2], Kajana Satkunendrarajah[2], Michael Fehlings[2]

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

MicroRNA-21 (miR-21) is among the most robustly upregulated microRNAs after spinal cord injury (SCI). However, the role of miR-21 in SCI pathobiology is not fully understood. A screen of circulating microRNAs in patients with non-traumatic SCI (ntSCI), found that expression of miR-21 is correlated to the severity of neurological dysfunction and the extent of residual deficits after treatment. We hypothesized that miR-21 is related to the underlying pathobiology of ntSCI, and that downregulation of miR-21 may improve ntSCI outcome. To examine this hypothesis, wild-type (WT) and miR-21 Knockout (KO) mice were assigned to either sham or injury groups (n=7/group). For injury groups, a biomaterial that causes bone deposition was placed under the C5-C6 laminae, causing gradual compression of the cervical spinal cord. Mice were assessed for motor deficits using Catwalk gait analysis, the rotarod test, and the Schnell swim test. Immunohistochemistry for Iba1+ microglia, GFAP+ astrocytes and NeuN+ neurons was performed. Deletion of miR-21 improved performance on the rotarod by 70% compared to WT ntSCI mice ($p<0.01$). MiR-21 KO ntSCI mice were significantly faster than WT, and were indistinguishable from shams in the swim test. Iba1+ microglia were reduced by 45% in the compressed region of miR-21 KO mice compared to WT spinal cords ($p<0.001$). In summary, KO of miR-21 reduced inflammation and resulted in motor preservation relative to WT animals. Therefore, miR-21 and its target genes appear to be relevant to ntSCI pathobiology, and may provide therapeutic targets for future research.

3-C-65 Amyloid-Beta Oligomers Impair Presynaptic Differentiation by Interfering Beta-Neurexin Protein Complexes

Alfred Lee[1], Yusuke Naito[1], Husam Khaled[2], Hideto Takahashi[3]

[1]Institut de recherches cliniques de Montréal/ McGill University, [2]Institut de recherches cliniques de Montréal/ Université de Montréal, [3]Institut de recherches cliniques de Montréal

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases. Amyloid-β (Aβ) is a key molecule involved in AD pathogenesis such as synapse loss and synaptic dysfunction. Neurexin (NRX) is a neuronal cell adhesion molecule which is crucial for presynaptic development and maturation. Our recent study has uncovered that Aβ oligomers (AβOs) directly bind to β-isoform of NRXs at their N-terminal histidine rich domain (HRD), resulting in a decreased NRX1β expression on the axon surface and NRX-mediated presynaptic differentiation. However, the underlying mechanisms are poorly understood. We performed an internalization assay using hippocampal neurons expressing HA-tagged NRX1β with AβO treatment. Our data suggest that AβOs facilitate NRX1β internalization in axons through interacting with NRX1β HRD. In addition, we uncovered a novel protein, known to regulate NRX1β surface expression, which binds to HRD of NRXβs by performing an in situ surface binding assay. Since this NRXβ interactor and AβOs bind to the HRD of NRX1β, we applied AβOs and the NRXβ interactor in a dose-dependent manner. Strikingly, the NRXβ interactor significantly dampened AβOs binding to NRX1β suggesting that the novel protein and AβOs competitively interact with HRD of NRX1β. Furthermore, overexpression of the NRXβ interactor in axons rescued Aβ-mediated reduction of presynaptic differentiation. In conclusion, our data suggest that AβOs decrease NRX1β-mediated presynaptic differentiation due to NRX1β internalization by interfering NRX1β protein complexes.

3-C-66 The metabolic regulator p66Shc as a therapeutic target for Alzheimer's Disease

Asad Lone[1], Robert Cumming[2]

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

The amyloid hypothesis has dominated drug discovery and therapeutic strategies in Alzheimer's disease (AD) for the last 20 years, regardless of several unsuccessful clinical trials. A significant population of the elderly have pronounced amyloid beta (Aß) deposition within their brains, yet show no symptoms of dementia, indicating that some cells are resistant to Aß toxicity. Several studies suggest that CNS cells that are resistant to Aß toxicity display a metabolic shift from mitochondrial-dependent oxidative phosphorylation (OXPHOS) to aerobic glycolysis for their energy needs. Expression & activation of the adaptor protein p66Shc has been shown to shift the cellular metabolic state from OXPHOS to aerobic glycolysis. Hence, we propose that the expression & activation of p66Shc in neuronal and glial cells promotes both increased OXPHOS

and sensitivity to Aß toxicity. Expression and activation of p66Shc repressed glycolytic enzyme expression and increased mitochondrial electron transport chain activity and ROS levels. The opposite effect was observed when endogenous p66Shc expression was knocked down. Activation of p66Shc increased sensitivity to Aß toxicity, whereas silencing p66Shc protected cells from Aß insult. Preliminary data hints to p66Shc's metabolic & protective effects being mediated through the transcription factor NRF2. Thus, expression and activation of p66Shc renders CNS cells more sensitive to Aß toxicity by promoting mitochondrial OXPHOS and ROS production, and p66Shc may represent a potential therapeutically relevant target for AD.

3-C-67 Metformin results in hippocampal remodeling and improved memory encoding in paediatric brain tumor survivors treated with cranial radiation: A pilot randomized controlled crossover study

Ramy Ayoud[1], Freda Miller[2], Kiran Beera[1], Cynthia de Medeiros[1], Suzanne Laughlin[1], Eric Bouffet[1], Donald Mabbott[1]

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

Curative cranial radiation results in hippocampal and memory insult in children with brain tumours. Metformin stimulates hippocampal neurogenesis and improves memory in mice. We conducted a pilot double blind randomized controlled cross-over trial to examine feasibility and test the effects of metformin versus placebo on hippocampal volume and declarative memory in pediatric brain tumor survivors treated with cranial radiation. 24 participants (Age = 13.96 ±3.51) (M = 14, F = 7) were randomly assigned to complete consecutive 12-week cycles of Metformin (A) and Placebo (B) in either an AB or BA sequence: 10-week washout occurred at crossover. At baseline and immediately following treatment for each condition we obtained: (a) structural MRI to obtain overall/subfield hippocampal volume and (b) tests of memory. Linear mixed modelling was used to test the effects of treatment condition and time on difference from baseline scores: An interaction term was used to test for carryover. Adherence was high and participants tolerated metformin. No change in overall hippocampal volume was observed bilaterally - but increased volume in the right subiculum and fimbria was evident for metformin vs. placebo (ps < .05). Notably, decreased right CA3 volume was evident for metformin carryover - suggesting a remodeling of hippocampal structure. Treatment with metformin resulted in improved memory encoding (p's < .05). Metformin may be effective for normalizing hippocampal structure and memory encoding in pediatric brain tumor survivors and warrants consideration in larger trials.

3-C-68 Depressive etiology of chronic traumatic encephalopathy in anterior cingulate white matter

Sarah Rind[1], Ian Mahar[1], Rebecca Mathias[1], Jonathan Cherry[1], Ann McKee[1]

[1]Boston University

BACKGROUND Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease involving cognitive, behavioral, and psychiatric symptoms. CTE involves accumulation and progressive spread of pTau thoughout the brain, which has been associated with neuroinflammation. However, the etiology of depressive CTE symptoms is still unclear. Among brain regions of interest, Brodmann area (BA) 25 (subcallosal cingulate) white matter has been implicated in depression and suicide, yet has not been examined in relation to CTE. METHODS Fixed BA25 samples were obtained from the VA-BU-CLF Brain Bank (N=43), including controls and CTE cases with and without depressive symptoms. Sections were stained for glial, neuronal, inflammatory, vascular, and pathological markers. Stained slides were digitally scanned and traced, and staining was quantified using a Leica Aperio system. RESULTS IBA1-expressing cells in BA25 white matter were highly increased in CTE cases relative to controls. For the first time in this region, AT8 and AB4G8 staining were identified in CTE cases, and the latter was significantly increased for depressed suicides in particular. pTDP43 immunoreactivity was not observed. CONCLUSIONS These are the first findings indicating microgliosis, inflammation, and pathological hallmarks in BA25 white matter for CTE cases, suggesting that localized changes in these markers may underlie depressive phenotypes in CTE. We are currently assessing white matter integrity in this region to determine if this is particularly altered for depressed CTE cases.

3-C-69 A new model for repeated concussion can cause acute neurologic impairment without structural damage in juvenile rats

Alicia Meconi[1], Ryan Wortman[1], David Wright[1], Sandy Shultz[1], Brian Christie[1]

[1]University of Victoria

Repeated concussion is becoming recognized as a serious public health concern around the world. Moreover, there is a greater awareness among health professionals for the potential of pediatric concussion to detrimentally alter the developing brain. To better study this issue, we developed an awake closed head injury (ACHI) model that enabled a mild closed head injury to be performed in awake juvenile rats. A modified neurological severity score (NSS) was used

immediately after each ACHI to examine cumulative effects of repeated injury on level of consciousness, and basic motor and reflexive capacity. Here we show that we can reliably produce repeated ACHI (4 impacts in 2 days) in both male and female juvenile rats without significant mortality or pain. Single and repeat injuries produce acute neurological deficits resembling clinical concussion signs, which can be quantified using the NSS. Behavioural analyses indicate repeated ACHI acutely impaired spatial memory in the Barnes maze, which correlated moderately with poorer NSS performance in females. Further behavioural examination using the Rotarod, open field, and elevated plus mazes did not reveal acute motor or emotional changes. Structural magnetic resonance imaging (MRI) indicated that repeated ACHI did not produce significant structural damage or volumetric loss in the cortex, hippocampus, or corpus callosum of animals at 1 or 7 days after ACHI. Together these results indicate that the ACHI model can provide a reliable, high throughput means to study the effects of concussion in juvenile rats.

3-C-70 Alpha-mangostin attenuates inflammation induced by systemic LPS administration in C57BL/6J mice and ameliorates memory deficits in a transgenic mouse model of Alzheimer´s disease

Miryam Nava-Catorce[1], Goar Gevorkyan[1], Gonzalo Acero[1]

[1]Universidad Nacional Autónoma de México

In this study, we evaluated the anti-inflammatory effect of α-mangostin (α-MG) on neuroinflammation induced by peripheral LPS administration in C57BL/6J mice and its capacity to ameliorate memory deficits in a triple-transgenic mouse model of Alzheimer´s disease (3xTg-AD). Methods. Young C57BL/6J mice were administrated by daily oral gavage with vehicle or α-MG (40 mg/kg) for 14 days. Then, three daily injections of LPS were applied to both groups. In addition, 12-month-old 3xTg-AD mice were administrated with α-MG (40 mg/kg) or vehicle by daily oral gavage for 7 weeks. Results. We observed that α-MG treatment diminished diarrhea and conjunctivitis signs observed in mice after the LPS administration. In the brain, we found that α-MG attenuated the increase in IL-6 and COX-2 protein levels induced by LPS-treatment. In addition, we demonstrated that α-MG decreased TSPO expression, a glial activation marker, in brain from LPS-treated mice. Interestingly, we found that the increase in TSPO and COX-2 expression occurred in vascular endothelial cells from LPS-treated mice. On the other hand, we found that 3xTg-AD mice administrated with α-MG performed better than vehicle-treated mice in a novel object recognition test. In summary, we show that α-MG can attenuate

neuroinflammation induced by peripheral LPS administration in C57BL/6J mice by reducing brain IL-6, COX-2 and TSPO levels. Our results suggest that α-MG attenuates vascular endothelial cell activation induced by LPS administration. Also, we found that α-MG is able to ameliorate memory impairment in 3xTg-AD mice.

3-C-71 Non-amyloid Beta Impacts of Presenilin in Alzheimer's Associated Olfactory Deficits

Mahraz Parvand[1], Tahereh Bozorgmehr[1], Dawson Born[1], Catharine Rankin[1]

[1]University of British Columbia

Objectives: Olfactory deficits are a primary symptoms of Alzheimer's disease (AD). The most common cause of familial AD is mutations of presenilin (PS) genes. We used the homologue of PS1 in C.elegans, sel-12, to study the cellular functional effects of these mutations. Methods: As C.elegans are innately repulsed by octanol and attracted by diacetyl, we utilized these odorants in chemotaxis assays to assess olfaction. Imaging was used to screen for morphological abnormalities in the C.elegans' ASH neurons which are responsible for detecting octanol. Results: C.elegans sel-12 mutants presented olfactory deficits from time of hatching and this deficit increased as worms aged, in a fashion similar to the neurodegenerative progression of AD. Introducing human wild-type PS1 into either the nervous system or specific neurons of C.elegans rescued olfactory defects, whereas familial PS1 mutations that affected Notch signalling did not, and mutations that left Notch intact also rescued. Thus there was functional homology between the human and the C. elegans genes. Lastly, imaging of neuronal morphology in sel-12 mutants showed increasing neuronal degeneration over time in ASH. Conclusions: Mutations in C.elegans homologue of PS1 are associated with altered olfaction that was rescued by wild-type human PS1, allowing us to assess how mutations in PS1 affect its function at the level of single neurons. As C.elegans do not have an amyloid-beta gene, this model allows us to investigate the non-amyloid beta impacts of PS1 in a behavioural phenotype that occurs as a symptom in AD.

3-C-72 Comparing spatial normalization methods on brain MRI data in the presence of MS lesions on real and simulated data

Salina Pirzada[1], Nasir Uddin[1], Chase Figley[1], Teresa Figley[1]

[1]University of Manitoba

Multiple sclerosis (MS) is a neurodegenerative disease characterized by demyelinated white matter (WM) lesions in the brain. The location of the lesions is thought to be linked with disease severity and state. However, analysis and interpretation of MRI data is based on spatial normalization, that were developed for healthy populations which may be less effective on diseased brains, due to the presence of lesions. In this work, we evaluated the performance of 4 commonly used spatial normalization approaches (i.e., linear warping, and three nonlinear warping methods: SPM's CAT12, FSL's FNIRT and MRIStudio's LDDMM) using both real and simulated data. Moreover, we compared the effect of lesion filling on the performance of such methods. To do so, MPRAGE and FLAIR images were acquired from 20 MS patients using a 3T Siemens MRI System. Normalization methods were separately applied to each patient's skull-stripped brains with and without lesion filling. The coefficient of variation maps, lesion volumes and paired t-tests between subjects for each normalization method suggest: nonlinear warping methods systematically outperformed linear warping, and SPM's CAT12 algorithm outperformed both FSL's FNIRT and MRIStudio's LDDMM non-linear algorithms while FSL's FNIRT had the most variance and was impacted the most by lesion filling. Lesion filling prior to normalization improved the accuracy of all three nonlinear approaches, but this effect was small compared to differences between normalization algorithms.

3-C-73 Testing the Robustness of Promising Neuro-Protective Drug Candidates in a Cervical Hemi-Contusion Model of Rats

Ward Plunet[1], Ward Plunet[1], Jie Liu[1], Elizabeth Raffaele[1], Suhana Kamakari[1], Oscar Seira[1], Kathleen Kole[1], Yuan Jiang[1], Lowell McPhail[1], Wolfram Tetzlaff[1]

[1]University of British Columbia

A significant number of FDA approved drugs have demonstrated efficacy in preclinical spinal cord injury (SCI). These studies predominantly used thoracic models and treat within one hour after injury. However, most human injuries occur at the cervical levels and the short windows of intervention used in animal studies are difficult to translate in human trials. We therefore decided to assess the effects on functional recovery of the most promising FDA approved drugs when these are administered 3 hours after a cervical spinal cord hemi-contusion injury with the goal of finding robust treatments that could be taken forward into clinical trials. In 5 experiments, we tested 9 different FDA approved drugs (riluzole, valproic acid, fluoxetine, metformin, inosine, rosuvastatin, acetyl-l-carnitine, glibenclamide, tamoxifen) that had been

previously reported to improve functional recovery in SCI models. None of the 9 treatments improved recovery compared to control groups. Of the nine treatments tested only glidenclamide improved the amount of spared spinal cord tissue. RT-PCR measurements of mRNA expression changes of injured spinal cord tissue in the five drugs we have done short-term studies for indicate appropriate changes in gene expression for all treatments indicating the drugs are biologically active at the injury site. As in previous replication studies, establishing robustness in preclinical models is challenging and possible reasons will be discussed. Supported by the Rick Hansen Foundation through the ICORD-Rick Hansen Institute-Blusson Integrated Cure Partnership.

3-C-74 Association between peripheral neuroinflammation and DATSCAN data of the striatal nuclei in PD patients

Hossein Sanjari Moghaddam[1]

[1]*Tehran University of medical sciences*

The etiopathology of Parkinson disease (PD) and several other neurodegenerative diseases is inseparable from inflammatory processes, both cerebral and peripheral. Peripheral neuroinflammation has been postulated to be involved in the initiation and progression of PD. Neuotrophil to lymphocyte ratio (NLR) is an excellent marker of peripheral neuroinflammation. Herein, the association between NLR and dopaminergic loss in SN is investigated. Method: DATSCAN was applied to assess the dopaminergic loss in brain of 391 PD patients and 151 healthy controls. Once the blood sample was collected, neutrophil to lymphocyte ration (NLR) were calculated by autoanalyser device on participants' whole blood samples. Results: Our findings indicated that older age was correlated with more DAT deficit in the normal group but not in PD group. Furthermore, longer disease duration predicted lower SBR scores in the putamen of PD group. NLR was significantly correlated with caudal SBR in individuals with PD, even after adjustment for age and disease duration. NLR could not predict putaminal SBR in PD patients after adjusting for age or age and disease duration or SBR in neither of striatal regions after adjustment for age and sex in control groups Conclusion: based in our findings, it is believed that peripheral inflammatory processes play a notable role in the pathogenesis of PD. NLR as an excellent representative for peripheral neuroinflammation, could be considered a potential candidate biomarker for PD.

3-C-75 Motor cortical circuit interactions in Parkinson's disease

James Saravanamuttu[1], Natasha Radhu[1], Kaviraja Udupa[2], Carolyn Gunraj[1], Julianne Baarbé[1], Robert Chen[1]

[1]University Health Network, [2]National Institute of Mental Health and NeuroSciences

Short interval intracortical inhibition (SICI), short interval intracortical facilitation (SICF) and short latency afferent inhibition (SAI) are cortical circuits elicited by transcranial magnetic stimulation (TMS) that assess GABA-Aergic, glutamatergic and cholinergic function, respectively. Previous work has established that these circuits are aberrant in patients with Parkinson's disease (PD). The interactions between these circuits can be tested using triple-pulse TMS paradigms. However, these interactions have not been studied in PD. 14 PD patients (65.1±8.0 years) were studied ON and OFF dopaminergic medication. 14 healthy participants (64.4±7.3 years) served as controls. Surface electromyography measured first dorsal interosseous motor evoked potentials generated by TMS of M1. The interactions between SICI and SICF were evaluated by comparing SICF alone to SICF in the presence of SICI. The interactions between SAI and SICI were evaluated by comparing SAI alone to SAI in the presence of SICI and by comparing SICI alone to SICI in the presence of SAI. SICI in the presence of SAI was disinhibited in PD ON, PD OFF and controls. SAI in the presence of SICI was disinhibited in PD ON, PD OFF and controls. SICF in the presence of SICI was facilitated in controls, but not in PD ON or PD OFF. Our findings suggest that the interactions between SICI and SAI are preserved in PD, but the facilitatory effect of SICI on SICF is diminished in PD and is not affected by dopaminergic medications. Altered interaction between cortical circuits may contribute to the pathophysiology of PD.

3-C-76 Isolation and Characterization of Heterogeneous Amyloid Beta Oligomer Populations Using Size Exclusion Chromatography and Oligomer-Specific Antibody

Chih Chieh Shyu[1], Neil Cashman[1], Ebrima Gibbs[1]

[1]University of British Columbia

One of the greatest challenges in the study of Alzheimer's disease (AD) is the elucidation of causative agent in disease. Evidence implicates Aβ oligomers (AβO) as the causative agent leading to progressive neurodegeneration in AD, particularly low molecular weight (LMW) populations, which have been shown to impair synaptic transmission and cause cell death. AβOs can also travel long distances in the brain, leading to seeding of new disease foci and inducing cytotoxic insults. Great efforts are being made in understanding the structural and functional

biology of the various AβO isoforms, with the goal of developing targeted therapeutics. However, rapid aggregation of monomeric Aβ in solution hampers efforts to identify specific disease-causing AβO. It is thus imperative to develop a method to reliably identify and isolate individual subpopulations of AβOs. In my project, size exclusion chromatography (SEC) will be used to separate the heterogeneous mixture of Aβ monomers and oligomers and collect the different populations according to apparent sizes. Subsequently, surface plasmon resonance (SPR), a state-of-the-art label-free technology that can monitor protein-protein interactions in real-time, will be employed to determine the specificity of an AβO-specific monoclonal antibody (mAb), 5E3, a proprietary antibody developed in-house targeting the unique cSNK loop that is solvent-exposed only in AβOs.

3-C-77 Mouse models to explore genetic underpinnings of Developmental coordination disorder (DCD)

Jeffy Rajan Soundara Rajan[1], Kamaldeep Gill[1], Jill Zwicker[1], Daniel Goldowitz[1]

[1]University of British Columbia

Developmental coordination disorder (DCD) is a common neurodevelopmental disorder characterized by difficulties in motor performance and motor learning, which significantly interferes with activities of daily living and academic achievement. Evidence suggests DCD is highly heritable and phenotypically heterogeneous; however, little is known about the genetic underpinnings of DCD. This study aims to understand the phenotypic differences in inbred strains of mice and their ability to learn motor skills that mimic the human condition of DCD. A total of 12 different BXD recombinant inbred lines, along with the two parental strains B6 and DBA, have been used to explore this issue. We conducted three phases of phenotyping: Neurodevelopmental battery, General Motor Testing (gait analysis, rotarod, open field), and Motor Learning (horizontal ladder rung walking, complex wheel, accelerating rotarod, and skilled reaching task), designed to focus on similarities to the symptomology of the human condition of DCD. To validate developmental deficits, neonatal reflexes were evaluated, which revealed a spectrum of delays in onset. General motor testing and skilled motor learning tests revealed a wide range of differences from excellent to poor over consecutive days of testing. Analysis is ongoing to validate a phenotypic platform in mice that provides insights into the genetics of DCD. On a clinical level, the findings of this study have the potential to inform the development of interventions that may be used to improve outcomes in children with this disorder.

3-C-78 Direct comparison of MRI based myelin measurements in MS lesions and normal appearing white matter

Md Nasir Uddin[1], Teresa Figley[1], Ruth Ann Marrie[1], Chase Figley[1]

[1]University of Manitoba

Multiple sclerosis (MS) is a neurodegenerative disorder characterized predominantly by demyelinating white matter (WM) lesions in the brain. MRI enables non-invasive and indirect myelin estimation by employing different techniques including myelin water fraction (MWF) mapping, signal intensity ratio of T1- and T2-weighted images (T1w/T2w), and diffusion tensor imaging metrics such as fractional anisotropy (FA) and mean diffusivity (MD). However, these methods are not sensitive to myelin in a similar manner. In this work, we examined the relationship between MWF, T1w/T2w, FA, MD, and volumetric measures in WM lesions (WML) and in normal appearing WM (NAWM). We scanned 29 MS patients in a 3T MRI system using whole-brain 3D GRASE, 3D MPRAGE, T2w FSE, multiband SE-EPI, and FLAIR sequences. Image analyses were performed using MRIStudio, SPM12, and MATLAB. Each subject's images were normalized to ICBM space using linear warping, followed by non-linear warping via the LDDMM algorithm. SPM's Lesion Segmentation Tool (LST) was used to segment and calculate the volumes of lesions for each patient. WML and NAWM region-of-interests (ROIs) were created from their binary masks in ROIEditor for each individual. GM and WM volumes were calculated using FSL SIENA. Compared to NAWM, WML showed higher MD but lower MWF, T1w/T2w and FA suggesting higher demyelination and/or axonal degradation happened in WML. Moreover, we found that MWF, T1w/T2w, MD and volumetric measures are all correlated and appear to be sensitive to myelin related changes in WML and NAWM in patients with MS.

3-C-79 Advances in familial multiple sclerosis genetics pave the way for novel neuroscience research

Carles Vilarino-Guell[1]

[1]University of British Columbia

Multiple sclerosis (MS) is a common inflammatory disease of the central nervous system characterized by myelin loss, varying degrees of axonal pathology and progressive neurological dysfunction. Environmental factors and allelic variants are known to contribute to MS susceptibility; however, through the implementation of second generation sequencing

technologies we have identified pathogenic mutations responsible for the onset of MS in multi-incident families. This study has lead to the identification of 14 genes with potentially pathogenic mutations for MS. Interestingly, these genes and mutations appear to cluster within linked immunological pathways underlying a common biological mechanism implicated for the onset of familial MS. These include three genes in the fibrinolysis and complement activation complex, four regulators of the Wnt signaling pathway, two genes involved in nuclear receptor complexes, two in the formation of the inflammasome, and three cation exchangers. The characterization of these mutations suggest a dysregulation in calcium/potassium homeostasis, and exacerbated cytokine/chemokine synthesis and inflammatory response as the underlying biological mechanism for familial MS. Further analysis of these genes, pathways, and cellular and animal models based on these mutations will offer unparalleled insight into the molecular mechanisms leading to the onset of MS. These mutations also provide the means for the generation of novel cellular and animal models for neuroscience research, in which to develop new and more effective treatments.

3-C-80 The effects of SDC3 and FGFRL1 on neurodegeneration in AD and PD

JUELU WANG[1], Weihong Song[1]

[1]University of British Columbia

Neuritic plaque, the pathological hallmark of Alzheimer's Disease (AD), is formed by extracellular deposits of amyloid â protein (Aâ) cleaved from amyloid â precursor protein (APP). Parkinson's Disease (PD) is featured by intracellular Lewy bodies (LBs), primarily consisted of aggregated alpha-synuclein protein (áSyn), encoded by SNCA gene. AD and PD are characterized by cholinergic neuronal loss in basal forebrain and nigrostrital dopaminergic deficient, respectively. In this study, we stably overexpressed human wildtype/ mutant APP and SNCA in the cholinergic SN56 and dopaminergic MN9D cells. Gene expression profiling was performed in APP-related and SNCA-related stable cells, respectively. SDC3 gene was differentially expressed in SN56-APPSWE and MN9D-APPSWE cells, while FGFRL1 gene was differentially expressed in SN56-SNCAA53T and MN9D-SNCAA53T cells. In the APPSWE knock-in mice, SDC3 protein level was significantly increased in medium septal compared with substantial nigra. Knockdown of SDC3 gene showed protective effects in SN56-APPSWE cells under hydrogen peroxide treatment, but not in MN9D-APPSWE cells. Meanwhile, FGFRL1 protein level was upregulated in dopaminergic but not cholinergic neurons in the SNCAA53T transgenic mice. Knockdown of FGFRL1 gene only rescued cell death in MN9D-SNCAA53T cells under hydrogen peroxide treatment, but not in

SN56-SNCAA53T cells. Taken together, differential expression of SDC3 and FGFRL1 in the cholinergic and dopaminergic neuron may mediate the selective neurodegeneration in APPSWE-associated AD and SNCAA53T-associated PD.

3-C-81 Double-Tap: A novel high-throughput machine vision behavioural paradigm to study sensorimotor gating using Caenorhabditis elegans

Anna Willms[1], Troy McDiarmid[1], Catharine Rankin[1]

[1]University of British Columbia

The ability to filter out irrelevant stimuli and amplify salient sensory information is critical for survival. In line with this, deficits in sensorimotor gating are observed in diverse neuropsychiatric disorders. Prepulse inhibition is a decrease in magnitude or probability of a startle response which occurs when a weak pre-pulse stimulus is delivered 30-500ms before a startling pulse stimulus. When the inter-stimulus interval is longer, prepulse facilitation is observed as an increase in magnitude or probability of the startle response. The mechanisms of prepulse facilitation remain largely uncharacterized. We employed automated machine vision behavioural tracking to establish a novel high-throughput paradigm to investigate prepulse facilitation and inhibition in the genetic model organism Caenorhabditis elegans. Prepulse facilitation is observed at long inter-stimulus intervals (200-500ms) between the pre-pulse stimulus and pulse stimulus that mirror intervals observed in other invertebrate and mammalian species. Prepulse inhibition is transiently observed when very weak pre-pulse stimuli are used. A candidate genetic screen of monoamine mutants suggests a role for both dopamine and serotonin in prepulse facilitation. We are currently carrying out optogenetic activation of serotonin and dopaminergic neurons to provide positive evidence to support this observation. The high-throughput nature of our prepulse facilitation paradigm will enable a molecular understanding of how neuropsychiatric disorder associated genes disrupt normal sensorimotor gating in vivo.

3-C-82 Functional Variomics Group: Analysis of ASD-associated PTEN gene variants in hippocampal neurons

Riki Dingwall[1], Matthew Edwards[1], Danya Abazari[1], Kathryn Post[1], Fabian Meili[1], Manuel Belmadani[1], Benjamin Callaghan[1], Payel Ganguly[1], Troy McDiarmid[1], Kurt Haas[1], Chris Loewen[1], Paul Pavlidis[1], Douglas Allan[1], Timothy O'Connor[1], Catharine Rankin[1], Shern

[1]University of British Columbia

Autism Spectrum Disorder (ASD) is a collection of neurodevelopmental disorders with a large genetic component. Though all ASD patients share a core clinical phenotype, large heterogeneity in symptom severity and breadth, as well as the growing number of associated genes, has stymied a complete understanding of its aetiology. In total, 3375 genes have thus far been broadly associated with ASD. This is further complicated by the identification of 5299 ASD-associated variants reported affecting 3374 genes, the majority of which lack functional phenotyping. We are part of a seven-lab consortium combining high-throughput and high-resolution assays to test large numbers of ASD-associated genes and their multiple variants across a number of model organism systems. We initially focused on the ASD-associated gene PTEN (phosphatase and tensin homolog), a crucial negative regulator of the PI3K/mTOR pathway. We have functionalized 15 ASD-associated variants of PTEN in rat hippocampal neurons, focusing on changes to PSD-95 density, total dendrite length, and soma size. The majority of the ASD-associated variants tested were loss-of-function, if not across all of our metrics (9 of 15), then across some (4 of 15), with only a single ASD-associated variant capable of phenocopying wildtype PTEN across all of our measures.

3-C-83 Functional Variomics Group:High-volume functionalization of human autism PTEN variants in Drosophila

Payel Ganguly[1], Kathryn Post[1], Riki Dingwall[1], Matthew Edwards[1], Tianshun Lian[2], Troy McDiarmid[1], Manuel Belmadani[1], Ben Callaghan[1], Fabian Meili[1], Barry Young[1], Warren Meyers[1], Keneth Matreyek[3], Douglas Fowler[2], Sanja Rogic[1], Paul Pavlidis[1], Christopher

[1]University of British Columbia, [2]The University of British Columbia, [3]University of Washington

Clinical exome and genome sequencing is identifying variants in gene sequence at an increasing pace. However, the development of methods to determine whether variants are function-altering lags far behind and around ~50% of identified variants for any gene are designated as VUS (Variant of Unknown Significance). Our group is developing a multi-platform approach using numerous model systems, including Drosophila, Saccharomyces cerevisiae (yeast), C.elegans, rat and HEK293 cells to experimentally determine whether coding sequence variants are function-altering. We will present our analysis of ~100 human PTEN (hPTEN) variants that include established loss and gain of function mutants to calibrate assays, and also variants identified from non-diseased individuals, and those with either Autism Spectrum Disorder or cancer. These have all been integrated into flies as UAS-hPTEN transgenes into the attP2 locus

by phiC31 integrase. In flies, ubiquitous overexpression of 'wildtype' UAS-hPTEN resulted in phenotypes including a ~2-4 day delay to eclosion. By comparing eclosion delay for overexpressed UAS-hPTEN variants, we have assigned variants as wildtype, gain of function or loss of function (amorphic or hypomorphic). We will present these data and also comparisons of hPTEN functionalization data between the multiple model systems. Our work will demonstrate the utility of Drosophila as a powerful platform for high volume screening for the relative function of large numbers of human gene variants from healthy and diseased individuals.

3-C-84 Functional Variomics Group: Precise structure-function analysis of ASD associated gene variants in PTEN using targeted CRISPR gene replacement in Caenorhabditis elegans

Troy McDiarmid[1], Kathryn Post[1], Riki Dingwall[1], Payel Ganguly[1], Matthew Edwards[1], Ben Callaghan[1], Manuel Belmadani[1], Fabian Meili[1], Warren Meyers[1], Barry Young[1], Sanja Rojic[1], Chris Loewen[1], Douglas Allan[1], Timothy O'Connor[1], Shernaz Bamji[1], Paul Pavlidis

[1]University of British Columbia

A primary challenge facing Autism Spectrum Disorder genetics is the large and growing number of genes and gene variants of unknown functional significance. To determine the functional effects of ASD-associated variants we developed a novel strategy based on CRISPR-Cas9 genome engineering in the high-throughput genetic model organism Caenorhabditis elegans to generate single-copy integrated knock-in lines expressing the exact human gene variants identified in ASD. We have begun by focusing on the high-confidence ASD-associated gene PTEN. In C. elegans, the sole ortholog of PTEN, daf-18, regulates attractive navigation behaviour up a concentration gradient of NaCl (this behaviour is called NaCl chemotaxis). Using a novel automated machine vision chemotaxis paradigm we have shown that either directly replacing daf-18 with human WT PTEN using CRISPR or nervous system specific expression of human WT PTEN is able to substitute for loss of daf-18 and rescue this behavioural deficit. Surprisingly, all ASD-associated missense mutations in PTEN assessed resulted in partial or complete loss-of-function and failed to rescue this sensory deficit. Collaborative complementary in vivo functional assays in yeast, and fly as well as in vitro assays in HEK293 cells and rat neural culture directly corroborate our finding that ASD-associated PTEN variants are loss-of-function. The wealth of in vivo empirical data from this research will improve algorithms that estimate the pathogenicity of missense mutations, improve diagnostic accuracy, and further precision medicine efforts to treat ASD.

3-C-85 Functional Variomics Group: Precise structure-function analysis of ASD associated gene variants in PTEN using Saccharomyces cerevisiae

Kathryn Post[1], Barry Young[1], Fabian Meili[1], Benjamin Callaghan[1], Sanja Rogic[1], Catharine Rankin[1], Timothy O'Connor[1], Paul Pavlidis[1], Douglas Allan[1], Shernaz Bamji[1], Manuel Belmadani[1], Christopher Loewen[1], Kurt Haas[1]

[1]University of British Columbia

A primary challenge to understanding the underlying genetics of Autism Spectrum Disorder (ASD) is the large and growing number of genes and gene variants of unknown functional significance. High confidence ASD genes are classified due to identification of de novo likely gene disrupting (LGD) mutations in multiple, unrelated probands. However, the implications of these de novo mutations, as well as missense mutations identified within these same genes on neuron development and brain circuit formation are still not understood. To begin to understand the implications of these point mutations, we selected the ASD-associated phosphatase and tensin homolog gene, PTEN for initial study. We identified over 100 variants of PTEN, including 31 controls of various types and 70 variants known to be disease related. Following generation of these variants, we performed a synthetic dosage lethality (SDL) screen of wildtype human PTEN in Saccharomyces cerevisiae to identify genetic interactions of wildtype PTEN in yeast. Once genetic interactions were identified it was possible to test each variant's interactions to elucidate the impact of these variants compared to functional PTEN and a catalytically inactive PTEN variant. Additionally, protein stability of each variant was assessed to give a thorough understanding of PTEN-variant function and stability. Data from these experiments gives insight into the implications of point mutations on protein functionality and will influence investigations on the impacts of these variants on neuron and brain development as well as animal behavior.

3-D-86 Centrally evoked blood pressure changes after chemogenetic activation of serotonergic neurons in the rat

Katrina Armstrong[1], Mona Nazzal[1], Xiaoyu Chen[1], Larry Jordan[1], Katinka Stecina[1]

[1]University of Manitoba

Oscillations of arterial blood pressure (BP) are known to be strongly correlated with efferent sympathetic activity. These oscillations originate from the brain stem's "cardiovascular pacemaker circuit" and feedback involving the baroreceptor loop. However, the identity of brainstem neurons contributing to these rhythmic BP oscillations is unclear. In this study, we examined whether chemogenetic activation of a subset of serotonergic neurons in the caudal brainstem can induce rhythmic BP oscillations. Designer receptors exclusively activated by designer drugs (Gq-DREADDs) were used to selectively activate serotonergic neurons in the ventrolateral medulla. DREADDs were stereotaxically injected using adeno-associated viral vectors (AAV-hSyn-DIO-hM3Dq) into tryptophan hydroxylase-cre (Tph2-iCre) rats and were allowed to recover for 70-125 days. Acute experiments were performed in decerebrated (un-anesthetized) rats while recording lumbar ENG activity, arterial BP and lumbar field potentials from the surface of the spinal cord. Midbrain mesencephalic locomotor region (MLR) stimulation was applied to induce fictive locomotor activity in order to assess changes after applying DREADD actuators. In 8 animals (4=hM3Dq, 4=control), we found evidence for chemogenetic activation coinciding with larger arterial BP oscillations. Generally, spontaneous oscillations were greater in amplitude after chemogenetic activation while baseline BP and MLR-stimulation induced BP changes were variable.

3-D-87 Periaqueductal Grey Volume Associated with Neonatal Priming of Adult Paw Incision Pain

Sofia Assi[1], Simon Beggs[2], YuShan Tu[3], Lily Qiu[3], Arun Ramani[3], Shahrzad Ghazisaeidi[1], Michael Brudno[3], Jason Lerch[3], Michael Salter[1]

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

Children born preterm often undergo painful invasive medical procedures while in the neonatal intensive care unit (NICU). In adulthood, these children experience increased pain and hyperalgesia after subsequent surgery or injury in the same region in comparison to preterm-born adults whose neonatal surgeries were less invasive. We have modeled this phenomena using rodents of both sexes by giving an initial hind-paw incision at post-natal day 3 or 5, representing the invasive neonatal surgery of preterm children, followed by an additional hind-paw incision at adulthood (termed "double-incision"). Control animals that received only adult hind-paw incision are referred to as "single-incision". Mechanical hypersensitivity was measured using von Frey filaments before and 24 hours after adult incision. Double-incision rodents demonstrate a long lasting increased hyperalgesia (termed "pain priming") in comparison to

single-incision rodents. An unbiased search of the entire brain using a high-resolution 7T MRI imaging ex-vivo perfusion-fixed CD1 mouse brains revealed significant and robust volume change of the periaqueductal grey (PAG) in double-incision vs single-incision mice. This is consistent with previous studies that have shown volume expansion of the PAG in patients suffering from episodic migraines. Future studies will examine cellular and transcriptional changes within the PAG of mice and rats. These findings will greatly increase our understanding of the mechanics of pain priming phenomenon in neonates who spend their early life in the NICU.

3-D-88 "Graspability" Determines the Utility of Weber's Law in Evaluating the Visual Codes Supporting Grasping and Manual Estimation

Naila Ayala[1], Matthew Heath[1], Gordon Binsted[2]

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

Weber's law states that the just-noticeable-difference (JND) between two stimuli increases proportionally with stimulus magnitude. The law has been used to test the hypothesis that separate visual codes support actions and perceptions. Specifically, results have shown that grasping (i.e., action task) violates Weber's law, whereas manual estimations of target size (i.e., perceptual task) adhere to the law. Notably, recent work has proposed that reduced mechanical degrees of freedom in aperture shaping as a target approaches a participant's maximum aperture separation (MAS) limits the utility of Weber's law in examining the visual codes supporting actions and perceptions. The present study tested the biomechanics hypothesis by having participants grasp and manually estimate differently sized targets that were scaled to their individual MAS (i.e., 20% to 140% of MAS). These targets provided the opportunity to identify the 'knot' point associated with the utility of Weber's law in grasping and manual estimation. For all tasks, JNDs were computed via the within-participants standard deviations in peak grip aperture. Grasping JNDs did not systematically vary across the range of targets scaled 20% to 100% of MAS, and then decreased (i.e., from 100% to 140% of MAS). In contrast, JNDs for manual estimation increased linearly across the 20% to 140% range of MAS. Accordingly, our results demonstrate the utility of Weber's law in evaluating the dissociable visual codes supporting the grasping and manual estimation of functionally 'graspable' targets. Supported by NSERC.

3-D-89 The effect of pregabalin on neurological function following spinal cord injury

Erin Erskine[1], Ward Plunet[2], Nicholas Salterio[1], Wolfram Tetzlaff[2], Matthew Ramer[2], John Kramer[2]

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

Anticonvulsants like pregabalin are the first-line treatment for neuropathic pain caused by traumatic injury and non-traumatic diseases of the central nervous system. Recent evidence from a human cohort study suggests that early use of pregabalin after spinal cord injury (SCI) may result in improved motor scores, however, it is unknown to what extent changes in spinal neural circuitry are involved. Using a rat model of unilateral cervical contusion, we examined the effect of pregabalin treatment on both motor and sensory function and on changes to the spinal circuitry. For four weeks post-injury, rats were given daily pregabalin or filtered water through oral gavage. Motor and sensory functions were scored using the Montoya staircase assessment of fine motor skill and behavioural evidence of scratching, respectively. We found no significant relationship between the early administration of pregabalin and improved motor scores in the affected forelimb. However, rats receiving pregabalin had increased performance on the staircase task using their contralateral paw. Additionally, we found that self-injurious scratching, often displayed by animals with this type of injury, was greatly reduced in those treated with pregabalin. This led us to examine the activation of pruritic neurons in the dorsal horn above the level of injury. Our findings suggest that in rats pregabalin treatment has an at-time effect on pruritus and neuropathic pain, but contrary to the human cohort study, does not improve motor outcomes with early administration.

3-D-90 The Effects of Exercise-Induced Fatigue and Eccentric Muscle Damage on Kinesthesia

Gregg Eschelmuller[1], George Grose[2], Damian Manzone[3], Ryan Peters[2], Mark Carpenter[1], J. Timothy Inglis[1], Romeo Chua[2]

[1]University of British Columbia, [2]The University of British Columbia, [3]The University of Toronto

Exercise-induced muscle fatigue has been shown to impair kinesthesia. It remains unclear exactly how or where this disruption occurs and whether muscle spindles are implicated in the disruption of kinesthesia with fatigue. We used a movement task in which subjects (20) performed a slow (22 deg/s) extension of the right elbow through the horizontal plane without vision of the arm in one of two conditions. Subjects either had a motor pull their arm into extension (passive), or the subject eccentrically extended the arm (active). During elbow

extension, subjects opened the closed thumb and index finger of their right hand when they judged the hand to be passing through a specified target position. We investigated performance under conditions with and without mechanical vibration of the bicipital tendon, as well as before and after an eccentrically-based exercise protocol that induced fatigue in the biceps. Vibration of the bicipital tendon resulted in subjects opening their hand short of the target compared to the no-vibration condition. In the active conditions, after eccentric exercise, subjects undershot the target more than before exercise. However, in the passive condition, subjects performed with similar accuracy before and after exercise. In both conditions, pre and post exercise, mechanical vibration caused consistent undershooting of the target when compared with no-vibration trials. Our results suggest that the CNS continues to rely heavily on muscle spindles for kinesthesia, even when they reside in a muscle exposed to fatiguing eccentric contractions.

3-D-91 Characterization of neural activity in a hippocampus-like region of teleost fish brain in the context of active spatial navigation

Haleh Fotowat[1], James Jun[2], Candice Lee[3], Leonard Maler[3]

[1]Harvard University, [2]Columbia University, [3]University of Ottawa

Neural mechanisms underlying spatial navigation in aquatic vertebrates is largely unknown. Moreover, little is known about the relationship between encoding of spatial information and active sensing. Weakly electric fish Gymnotus Carapo use an active electric sense for spatial navigation in the dark. Their electric organ discharge frequency (EODf) is indicative of sensory sampling rate, and large transient increases in EODf is a hallmark of spatial learning. We used a wireless transmitter to record neural activity in the dorsal part of dorsal telencephalon- a region homologous to mammalian hippocampus- in freely navigating Gymnotus, while monitoring its EODf using electrodes placed in the water. The experiments were performed in the dark and fish's behavior was monitored using an infrared camera. We show that neurons in this region spike at very low rates and only during movement. Spikes largely occurred near landmarks or tank boundaries. Remarkably, an increase in EODf was observed on average following spikes of half of the recorded cells, indicating that activity in this region may cause an increase in sensory sampling rate. Moreover, many cells showed strong preference for spiking during backward swims. Backward swimming brings objects close to fish's head where largest number of electroreceptors are present and acts like foveation in mammals. Our results provide the first characterization neural activity a hippocampus-like region of weakly electric fish and sheds light

on the relationship between sensory sampling rate and higher order encoding of spatial information.

3-D-92 PAX6 Gene Therapy Rescues Corneal Defects in Mouse Model of Aniridia; a Rare Blinding Disorder

Jack Hickmott[1], Siu Ling Lam[1], Elizabeth Simpson[1]

[1]University of British Columbia

Introduction: Aniridia is a rare blinding disorder, caused by mutations in the gene paired box 6 (PAX6). Born with poor vision, vision loss advances in early adulthood due to glaucoma, corneal pannus, and keratopathy. Glaucoma can be managed, however corneal treatments fail to provide lasting vision. Gene therapy has become a successful treatment avenue for rare disorders. Here we conduct preclinical tests of a PAX6 gene therapy towards a new vision-saving treatment for the aniridic cornea. Methods: A 3xFLAG/PAX6 open reading frame was cloned into a recombinant adeno-associated virus (rAAV) genome, commercially packaged into rAAV9, and injected directly into the cornea of wild type (Wt) and Pax6Sey/+ (Sey, a model of aniridia) mice. Mice were monitored for one week and harvested for molecular biological and histological analysis. Results: rAAV transduces the cornea, with expression detectable within one week. Treated Sey mice had a significantly thicker corneal epithelium than untreated control Sey mice ($p<0.005$) and were not significantly thinner than Wt controls. Treated Sey corneas were populated by an intermediate number of epithelial cells: more than Sey ($p<0.01$) but less than Wt ($p<0.05$) controls. No significant reduction in epithelial thickness or the number of epithelial cells was detected in treated Wt mice. Significance: The preliminary success of PAX6 gene therapy paves the way for dose optimization, longitudinal study, and functional characterization.

3-D-93 Noxious heat pain processing is global phenomenon - a contact heat evoked potential study

Catherine Jutzeler[1], Armin Curt[2], Jan Rosner[2], Michele Hubli[2], John Kramer[1]

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

Contact heat evoked potentials (CHEPs) reflect cortical responses of A-delta nociceptors activated by noxious heat stimuli. Missing from the current understanding is whether the cortical

processing of these stimuli is dependent on the location of where the heat pain is evoked. The objective of the study was to determine whether the processing of repetitive noxious heat stimuli is dependent on the location stimulated (i.e., different dermatomes). To this end, CHEPs were acquired segmentally (i.e., dermatomes C4, C6, and C8) in 92 healthy individuals using normal and increased baseline stimulation protocols. For both stimulation protocols, mixed-effect models and bi-variate correlations were employed to assess the habituation to repetitive noxious stimuli, the variability in conduction velocity (i.e., latency jitter), and the relationship between CHEPs amplitude and pain rating. Our analysis revealed significant habituation to repetitive noxious stimulation and a strong correlation between rating and CHEPs amplitude within all dermatomes. No between-dermatome differences were found in these two outcomes. Lastly, the latency jitter was comparable between the three dermatomes. Employing increased baseline stimulation protocol markedly reduced the latency jitter in all dermatomes. Taken together, these results indicate that processing of repetitive noxious heat is independent of stimulation site (i.e., global phenomenon).

3-D-94 Does electrical vestibular stimulation circumvent the velocity storage?

Navid Khosravi-Hashemi[1], Anthony Chen[1], Oscar Ortiz-Angulo[1], John Kramer[1], Jean-Sebastien Blouin[1]

[1]University of British Columbia

Self-motion perception is a fundamental concern for our survival. The vestibular system contributes to our perception of motion: for example, the semicircular canals in inner ear sense angular motion of the head in space. The firing rate of primary vestibular afferents decays with a time constant of about 4s when exposed to a constant angular velocity stimulus, reflecting the canal-cupula dynamics. Further propagation of the canals signal occurs through a central neural integrator termed the velocity storage, lengthening the time constant to a constant angular velocity stimulus to around 15s. Electrical Vestibular Stimulation (EVS) is widely used to characterise vestibular processes and is assumed to mimic Kinetic Stimuli (KS). Here we ask if perceptual responses evoked by EVS and KS are centrally processed the same way. We developed a mathematical conversion model between KS and EVS based on reported transfer functions between EVS and KS to primary vestibular afferent firing rates. Equivalent EVS (virtual) and KS (real) rotation profiles were applied separately and participants were asked to report the perceived rotation by turning a handle connected to a potentiometer. Response time constant under KS was 13.8±2.2s agreeing with previous studies, but significantly lower under

EVS(7.4±1.0s, Wilcoxon Ranksum p=0.006). This suggests that the perception of rotation to EVS and KS are centrally processed differently and the lengthening effect of the velocity storage is not applied to perceptions of rotation induced by EVS.

3-D-95 Foot sole cutaneous signals modulate soleus tendon vibration reflex coupling during standing

Robyn Mildren[1], Gregg Eschelmuller[1], Jean-Sebastien Blouin[1], Mark Carpenter[1], J. Timothy Inglis[1]

[1]University of British Columbia

Feedback from somatosensory receptors within the triceps surae muscles and foot sole skin can be used for balance control. The aim of our experiment was to examine interactions between foot sole cutaneous feedback and soleus reflexes evoked by noisy Achilles tendon vibration during standing. In twelve healthy young adults, we delivered continuous noisy (10-115 Hz) vibration to the Achilles tendon and recorded surface EMG from the soleus muscle. We also delivered electrical pulse trains (five 1 ms square-wave pulses at 200 Hz) intermittently (every 0.8-1 s) to skin under the heel or metatarsals of the foot sole. We analyzed time-dependent (referenced to skin stimulus onset) coherence and cross-correlations between the noisy tendon vibration acceleration and rectified surface EMG. Coherence between the tendon vibration and EMG was seen across a bandwidth of ~10-70 Hz, and coherence was enhanced by metatarsal and suppressed by heel electrical stimuli. Metatarsal stimuli enhanced peak-to-peak cross-correlation strength at a 96 ± 14 ms latency (peak enhancement), while heel stimuli suppressed cross-correlation strength at a 119 ± 23 ms latency (peak depression). The effects of skin stimuli on coherence and cross-correlation strength did not appear to reflect the fluctuations in background EMG levels. The spatial, temporal, and frequency characteristics of foot sole cutaneous afferent control of stretch reflex transmission contributes to our understanding of sensorimotor integration during standing balance.

3-D-96 Towards CRISPR/Cas9-Mediated Gene Therapy to Correct Blindness in a Novel Mouse Model of Aniridia

Zeinab Mirjalili Mohanna[1], Siu Ling Lam[2], Tom Johnson[1], Tess Lengyell[1], Elizabeth Simpson[2]

[1]BC Children's Hospital Research Institute/ University of British Columbia, [2]University of British Columbia

PAX6 encodes a conserved transcription factor that controls many aspects of early development of the central nervous system, eye, and some non-neuronal tissues such as the pituitary and pancreas. Heterozygous loss-of-function mutations of PAX6 result in a rare congenital disorder, known as aniridia. Aniridia is a syndrome, but is best known for the iris hypoplasia visible in the child's eyes at birth. Currently, there is no cure or long-term therapy for aniridia. One possible approach to treating aniridia is gene-editing therapy. We hypothesize that CRISPR-mediated gene editing can increase the expression of PAX6 protein, improve the function of the neural and other tissues of the eye, and ultimately rescue the mutant phenotype. Towards this end, we created a new mouse model of aniridia using CRISPR technology to add a 3xFLAG "tag" on the Sey Pax6 gene. Such a tag will allow antibodies to distinguish the wild-type and CRISPR-corrected PAX6 proteins. The next objective was to carry out a cell-based optimization of guide RNAs (gRNAs) in Pax6 mouse embryonic stem cell cultures. Purified Cas9, template DNA, and several synthetic candidate gRNAs were delivered to the cells by electroporation. Functionality of each gRNA was first validated by Sanger sequencing, and then quantified by site-specific next generation sequencing. Excitingly, compared to the control, our best gRNA corrected the Pax6 mutation in 15% of the cells. Furthermore, initial studies show no mutagenesis of the wild-type allele. The next objective is to correct the Pax6-Sey mutation in vivo in our mouse model.

3-D-97 Development of the dedicated neural circuit for swimming in the Zebrafish (Danio rerio) spinal cord.

Yann Roussel[1], Tuan Bui[1]

[1]University of Ottawa

Locomotion is a fundamental task executed by the nervous system across vertebrates. However, the maturation process of locomotion during development is accompanied by changes in the nervous system. Understanding these changes will allow us to better understand how locomotion is controlled in mature individuals. Motor activity can be described as a precise pattern of muscle activation operating at specific rhythms. Some of these rhythms arise from dedicated spinal networks named central pattern generators (CPGs). Between 3-5 days post-fertilization (dpf), larval zebrafish show a rapid transition in their swimming movements. We investigated whether this transition was accompanied by changes in rhythm generating mechanisms driving 20 Hz tail beats oscillations during swimming (endogenous pacemaker cells

versus network-driven rhythm). Previous studies suggest that at 3 dpf, reciprocal inhibition, a well-established mechanism for CPG operation, is not involved in rhythm generation at this developmental stage. Our results show that blocking glycinergic neurotransmission completely disrupts the 20 Hz rhythm in 4 to 5 dpf fish while this observed only in caudal segments at 3 dpf. This suggests a transition in rhythm generation mechanism that starts caudally at 3 dpf and moves rostrally afterwards. Overall, our findings - supported by a computational model - support the idea of an operational shift from pacemaker-driven to a network-driven CPG that coincides with the transition of larval zebrafish from burst swimming to a more mature « beat-and-glide » swimming.

3-D-98 Differential effects of electrical vestibular stimuli on gait in Parkinson's disease

Stephanie Tran[1], Saurabh Garg[1], Mahsa Shafiee[1], Christina Jones[1], Martin McKeown[1]

[1]University of British Columbia

Postural instability is a cardinal symptom of Parkinson's disease (PD) that is largely resistant to treatment. Electrical vestibular stimulation (EVS) has been suggested to improve motor responsiveness when applied at low levels. To date, EVS has not been examined in people with PD while walking. We tested 14 PD (on-medication) and 12 healthy controls (HC). Monopolar stochastic vestibular stimulation (SVS) was applied to modulate the anterior/posterior (AP) plane and bipolar SVS was applied to modulate the mediolateral (ML) plane. Participants were blinded to stimulation and were required to walk down an electronic walkway. A dual task paradigm (serial-7 subtraction) was used. Ten gait parameters were assessed. Preliminary results show that PD were distinguishable from HC at baseline. When assessing individual parameters, there was a trend of decreased stride time variability in HC participants; however, the overall effect of stimulation was not obvious. Principal Component Analysis (PCA) was conducted to find the weighted linear combination of ten normalized gait parameters. Paired t-tests of the transformed data showed significance following only ML stimulation during single task in PD observed for double support and swing and dual task in HC for base of support (BOS), BOS variability and stride-time variability. Our study suggests that SVS-ML is capable of modulating gait however this is only evident when observing gait as a weighted combination rather than individual parameters. Further work is being conducted to understand the implication of this modulation.

3-D-99 Identification of active cortical networks during motor behaviour

Marc Vani[1], Timal Kannangara[1], Yingben Xue[1], Christine Denny[2], Diane Lagace[1]

[1]University of Ottawa, [2]Columbia University

The remapping of cortical networks after stroke is thought to subserve functional recovery. However, it has been challenging to identify with high temporal and spatial specificity which cells are active while performing motor tasks at various points during stroke recovery. Using inducible Arc-CreERT2 mice, this project is investigating what cells are functionally active during a motor task and when they are activated during recovery. By crossing Arc-CreERT2 and floxed-STOP-YFP mice, we can discriminate between networks activated at two time points in the same animal. For example, to determine if a cell within a network is reactivated at a future time, the animal is first administered 4OH-TAM in conjunction with a behavioural task to label activated cells with YFP. At a later time point, animals are given the behavioural task again, and sacrificed 90 minutes later so that endogenous Arc protein can be detected in the cells that are active at this later time. Immunohistochemistry for YFP and Arc reveals three discernable populations: 1) the neurons recruited at the first time point only (YFP+), the second time point only (Arc+), and at both time points (YFP+ Arc+). We have determined the optimal paradigm to label active networks in this model. This work therefore has begun to elucidate the cells that are active in motor areas during unilateral and bilateral motor tasks, and thus are foundational for differentiating how the cortical networks are modified during stroke recovery.

3-E-100 PVN CRH neuron anticipate innate coping strategies

Nuria Daviu Abant[1], Tamás Füzesi[2], David Rosenegger[1], Neilen Rasiah[1], Toni-Lee Sterley[1], Jaideep Bains[3]

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

Flight or freeze are instinctive responses to threat. These behaviors are one component of a broader stress response that includes the recruitment of hypothalamic PVN CRH neurons. Here we reveal an unexpected role for these neurons as pre-motor controllers of the flight response to threat. We used single fiber photometry to record in vivo calcium responses in PVN CRH neurons during the looming-shadow test. In response to simulation of a predator attack, naïve mice showed an active escape response to a shelter in 80% of the trials. This was coupled to an increase in calcium in CRH that preceded the behaviour. Further, we show that these behaviors, although instinctive, are also trainable. We show a differential entrainment of CRH neurons to an

uncontrollable (learned helplessness) vs controllable (learned avoidance) stress training protocol. Following controllable, but not uncontrollable stress, CRH neurons show associative learning. When challenged with a looming shadow, controllable stress subjects show an increase in CRH calcium and a flight response in 93% of trials, but uncontrollable stress subjects show a propensity for freezing in 75% of trials and no increase in CRH calcium. These findings show that CRH neurons encode preparatory signals for an active motor action in response to a threat, thereby establishing a link between PVN CRH neurons and instinctive survival behaviors. Furthermore, these findings demonstrate that behavioral training can modify instinctive behavior.

3-E-101 Fear and anxiety in the hypothalamus

Tamás Füzesi[1], David Rosenegger[2], Nuria Daviu[1], Neilen Rasiah[2], Jaideep Bains[3]

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

Corticotropin-releasing hormone (CRH) synthesizing neurons in the paraventricular nucleus of the hypothalamus (PVN) are the controllers for endocrine and behavioral responses to stress. To date, any information about the activity of CRH neurons during/after stress is due to secondary measures (hormone measurements, immediate early genes) that have weak temporal fidelity. 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. Following a week of recovery and handling we began performing experiments. Mice were exposed to a variety of challenges. In response to footshock, CRH neurons showed a robust and transient increase in the Ca2+. An increase in Ca2+ of similar magnitude was observed during handling of the animal. Exposure to any, non-homecage environment however, revealed to a sustained increase of the Ca2+ signal that persisted until the animal was returned to the homecage. Interestingly, while repeated experiments such as fear extinction or habituation concurred with an adjustment in the animal's behavior it was not reflected in the Ca2+ response. Moreover, context dependent fear retrieval, novel and habituated environments all induced a Ca2+ level rise at similar amplitudes. Here, for the first time we provide data about the in vivo activity of PVN CRH neurons in response to stress.

3-E-102 Short-Term Gonadectomy Alters the Morphology of Pyramidal Neurons in the Hippocampus and Medial Prefrontal Cortex in Male Rats

Eric Lawton[1], Lauren Isaacs[1], Ari Mendell[1], Craig Bailey[1], Neil MacLusky[1]

[1]University of Guelph

Circulating testosterone (T) levels gradually decline in ageing males, which may be associated with impairments in cognition and memory. The effects of androgen loss may in part be explained by changes to the hippocampus and medial prefrontal cortex (mPFC), two areas critical for cognition and memory. Previous work in our lab has shown that after orchidectomy (ORCH), the apical dendrites of pyramidal neurons in the CA3 region of the hippocampus undergo dramatic expansion compared to sham-operated controls. It remains unknown how rapidly these effects occur, or whether similar effects are observed in other regions of the brain, such as the mPFC. Whether the stress of surgery influences this response also remains to be determined. We hypothesized that the effects of ORCH may include contributions from both loss of T and surgically-induced stress. To test this hypothesis, pyramidal neuron morphology was analyzed in hippocampal subfields CA1 and CA3 and layer 2/3 of the mPFC, after sham surgery, or ORCH with or without T replacement. At 10 days post-surgery, dendritic branching in CA1 was relatively unaffected by either surgical stress or loss of T. Apical dendrite branching of both CA3 and mPFC neurons, however, was significantly greater in ORCH rats than in either ORCH/T replaced or unoperated male controls. The lowest level of branching was observed in the sham operated male controls. These results suggest a complex interaction between stress and T in the regulation of pyramidal cell morphology in areas of the brain critical for cognition and memory.

3-E-103 Neurogenic and Neuroimmune Consequences of Chronic Stress: Distinct Modulatory Roles of Estrogen Receptors Alpha and Beta

Rand Mahmoud[1], Rand Mahmoud[1], Jessica Chaiton[1], Stephanie E Lieblich[1], Carmen Chow[1], Paula Duarte-Guterman[1], Liisa AM Galea[1]

[1]University of British Columbia

The hippocampus displays remarkable plasticity across the lifespan and is particularly sensitive to the effects of chronic stress. Notably, chronic stress alters adult hippocampal neurogenesis and the neuroimmune environment. Importantly, previous research indicates that the outcomes of chronic stress in females is dependent on ovarian hormones. Here, we examined the receptor

mechanisms underlying the modulatory effects of estradiol on the neurogenic and neuroimmune consequences of stress. Adult female mice (C57BL/6) were ovariectomized or sham-operated, then given six weeks of daily subcutaneous injections of the ERα-selective agonist propylpyrazole-triol (PPT), ERβ-selective agonist diarylpropionitrile (DPN), estradiol (E2), or vehicle. Two weeks into hormone treatment, all mice received two injections of the DNA synthesis marker, bromodeoxyuridine (BrdU), then were assigned to four weeks of Chronic Unpredictable Stress (CUS), or to non-CUS conditions. The density of BrdU+ cells in the granule cell layer was examined, and hippocampal cytokine levels were quantified. Preliminary results suggest that CUS reduced the survival of BrdU+ cells, but this effect was prevented by E2, suggesting a combined role of ERs α and β. Further, CUS increased hippocampal interleukin-6 in ovariectomized mice, but this effect was prevented by E2 or PPT treatment, indicating that ERα activation may ameliorate inflammation in the hippocampus under chronic stress. Thus, estrogen receptor subtypes may differentially contribute to the neurogenic and neuroimmune consequences of chronic stress.

3-E-104 Genetic disruption of Adipose Triglyceride Lipase (ATGL) in mediobasal hypothalamic neurons induces overweight and metabolic disturbances.

Romane Manceau[1], Khalil Bouyakdan[2], Alexandre Fisette[1], Demetra Rodaros[1], Grant Mitchell[3], Stephanie Fulton[1], Thierry Alquier[2]

[1]CRCHUM - Univeristé de Montréal, [2]Centre de recherche du CHUM, [3]Centre de Recherche du CHU-Ste-Justine

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. 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 high fat-fed mice that maintain a healthy body weight compared to mice that become obese. In addition, ATGL expression in the MBH is increased in response to fasting. 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 (ARC) of male ATGL flox mice to KO ATGL specifically in neurons (ARC-ΔATGL). First, we validated that ATGL expression is reduced by 40% in ARC-ΔATGL mice compared to ARC-WT. We found that ARC-ΔATGL 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. Finally, chow-fed ARC-ΔATGL mice have an increased fasting glycaemia and mild glucose intolerance. Together, our findings suggest that the ATGL pathway in MBH neurons beneficially regulates glucose and energy homeostasis. Ongoing experiments are aimed at assessing whether ATGL regulates TG metabolism in hypothalamic neurons.

3-E-105 Effect of dietary fructose on synaptic plasticity at AgRP neurons

Mikayla Payant[1], Alex Hebert[1], Eleftheria Maratos-Flier[2], Melissa Chee[1]

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

Fructose consumption in the western diet has greatly increased due to the addition of sugars and high fructose corn syrup in processed food and soft drinks. This increase in dietary fructose parallels the rise in obesity and metabolic disorders. While fructose is primarily metabolized by the liver, it may also cross the blood brain barrier and the central administration of fructose can increase food intake. However, the critical brain regions and mechanisms underlying the effects of fructose on central energy balance remain unknown. We fed wildtype mice a high fructose diet (HFrD) for 8 weeks to test the effects of dietary fructose on central energy balance. HFrD-fed mice have increased caloric intake and gain more body fat compared to their chow-fed littermates. Interestingly, HFrD feeding also led to an increase in the expression of agouti related peptide (AgRP) in the hypothalamus. It is known that fasting can stimulate AgRP neurons and activation of AgRP neurons will stimulate feeding. In order to determine if dietary fructose may increase the activation of AgRP neurons, we performed patch-clamp recordings and found that HFrD fed mice have an increase in excitatory synaptic inputs at AgRP neurons. These findings suggest that synaptic plasticity at AgRP neurons may promote the obesogenic effects of dietary fructose. Subsequent studies will determine the onset of HFrD mediated synaptic plasticity and whether these effects are reversible upon the cessation of fructose consumption.

3-E-106 Sex differences in stress habituation modulate pre- and post-synaptic 5-HT1A receptor function.

Tristan Philippe[1], Yi Yang[1], Judy Chang[1], Alexandra Ferland[1], Victor Viau[1]

[1]University of British Columbia

Most of the basic research examining behavioural and neural responses to stress has focused on males, despite sex differences. Serotonin (5-HT) is a neurotransmitter systems implicated in stress and is sexually dimorphic. Considering that 5-HT is regulated by 5-HT 1A receptors, we hypothesized that habituation to stress affects 5-HT 1A receptor function differently in males and females. Male and female SD rats were exposed to a single or repeated restraint stress (2hr daily for 5 consecutive days) or no stress. Animals were then injected with the 5-HT 1A receptor agonist, 8-OH-DPAT, using hypothermia and corticosterone responses as physiological indices for changes in pre- and postsynaptic 5-HT 1A receptor function, respectively. Males and females habituated to the stress and showed significantly lower (45% and 40%, respectively) corticosterone on the fifth day of restraint. Habituation increased hypothermia in males, but not females, suggesting higher pre-synaptic 5-HT1A receptor function. Restraint and 8-OH DPAT agonism increased corticosterone in both males and females, suggesting changes in post-synaptic 5-HT 1A receptor transduction. GTPγS[35] and 8-OH[3] DPAT binding assays were performed to confirm changes in 5-HT1A receptor transduction and number. These data suggest that habitation to stress increases pre-synaptic 5-HT 1A receptor function and levels in males, but not females. This uncovers an important mechanism for stress habituation that occurs in males, but not females and elucidates why females have a higher risk of mood and anxiety disorders.

3-E-107 Colitis promotes anxiety through a CRF-R1 mediated suppression of central anandamide signaling

Haley Vecchiarelli[1], Kaitlyn Tan[1], Vincent Chaing[1], Maria Morena[1], Catherine Keenan[1], Martin Sticht[1], Kira Leitl[1], Winnie Ho[1], Min Qiao[1], Keith Sharkey[1], Matthew Hill[1]

[1]University of Calgary

There is a large degree of comorbidities between inflammatory diseases and stress-associated neuropsychiatric disorders. However, the mechanisms underlying these comorbidities have not been fully elucidated. Endocannabinoids regulate anxiety and inflammation, making them a potential candidate to investigate the mechanism of these comorbidities. We employed an animal model of colitis (intracolonic trinitrobenzene sulfonic acid) to explore the role of endocannabinoids in this process in adult male rats. We previously showed that levels of anandamide (AEA) were decreased in the amygdala, hippocampus and medial prefrontal cortex, at one week after the induction of colitis. Furthermore, colitis was associated with an increase in

fatty acid amide hydrolase (FAAH) activity in these regions, indicating that peripheral inflammation increases central AEA hydrolysis. We also saw an increase in anxiety like-behaviour in the elevated plus maze. We now show that this increase in anxiety can be reversed with an acute intracerebroventricular administration a FAAH inhibitor, which increases AEA levels. Additionally, central administration of an antagonist of the corticotrophin releasing factor receptor 1 (CRF-R1) during colitis reversed the AEA reductions in the amygdala and hippocampus, indicating that the AEA reductions relevant for the generation of anxiety during colitis are regulated through a CRF-R1-driven increase in FAAH activity. Together these findings add to the understanding of central mechanisms underlying anxiety-like behaviours associated with peripheral inflammation.

3-F-108 A Novel Iterative Screen in C. elegans Reveals a Protein in the Insulin Signaling Pathway to be a Key Mediator of Memory

Sylvia Almeida[1], Daniel Merritt[1], Glenn Wolfe[1], Afrin Bhattacharya[1], Justina Melkis[1], Derek van der Kooy[1]

[1]University of Toronto

Learning is a process in which an animal alters its behavioural response to a stimulus as a result of experience. The nematode worm Caenorhabditis elegans is capable of learning associations between sensory cues, but how this process occurs at a molecular level, and the biochemical identity of the memories, remain unknown. A forward genetic screen performed to identity novel genes involved in C. elegans associative learning implicated the gene lrn-3 in the pathway. lrn-3(mm200)(UT1306) worms exhibited an unusual suite of associative learning phenotypes affecting multiple sensory modalities: the animals could learn to associate starvation with cues sensed by only one of the two pairs of primary attractive olfactory neurons, and failed to associate starvation with cues sensed by the primary taste neurons. None of the learning deficiencies observed were due to an inability to sense the stimuli. Genome sequencing revealed lrn-3(mm200) to be allelic to akt-1/Protein Kinase B, a serine/threonine kinase in the insulin signaling pathway. A transgenic line expressing wild type akt-1 on an extrachromosomal array fully rescued benzaldehyde-starvation associative learning, a type of learning that is impaired in lrn-3(mm200) worms, in the UT1306 strain. In the future, we aim to identify downstream targets of AKT-1 during associative learning and determine which cell(s) its expression is necessary in during this process to more fully elucidate the role of insulin signaling in C. elegans associative learning.

3-F-109 Emotional Memory in Bipolar Disorder and Major Depressive Disorder: A Preliminary Report

Bryce Bogie[1], Monisha Persaud[1], Flavio Kapczinski[1], Benicio Frey[1]

[1]McMaster University

Introduction: Bipolar disorder (BD) and major depressive disorder (MDD) are associated with memory recall deficits for emotional information. While emotionally positive and negative information is preferentially recalled by healthy controls (HC), individuals diagnosed with MDD display a recall bias towards emotionally negative information. Recall for emotionally positive and negative information in BD is blunted and emotionally neutral information is preferentially recalled. We aimed to be the first to compare emotional memory performance between BD, MDD and matched HC. Methods: All participants completed clinical assessment measures to confirm their eligibility, including the SCID. All participants in the MDD and BD groups met criteria for past MDD and BD I, respectively, but were currently euthymic. Participants completed an encoding task that involved rating the emotional intensity of charged (positive, neutral and negative) images. Participants returned 1 week later for a surprise recognition memory task. Results: Each group reacted more intensely to positive and negative images versus neutral images. Overall memory accuracy scores revealed that the MDD group correctly recalled more negative images, the BD group correctly recalled more neutral images and the HC correctly recalled more positive images. Conclusion: The reactivity trends for MDD and BD did not align with the observed memory trends. Individuals with past MDD and BD may have a reactivity bias similar to HC and an emotional memory bias consistent with individuals in a current depressed or manic state.

3-F-110 Dissociable structural and functional hippocampal outputs via distinct classes of cells in the subiculum

Mark Cembrowski[1], Matthew Phillips[1], Salvatore DiLisio[1], Brenda Shields[1], Nelson Spruston[1]

[1]Howard Hughes Medical Institute

The mammalian hippocampus participates in a variety of behavioral and cognitive functions. It has been postulated that parallel circuitry, embedded within the serial architecture of the

hippocampus, may give rise to such functional diversity. We aimed to identify, delineate, and manipulate such putative parallel architecture in the dorsal subiculum, the primary output subfield of the dorsal hippocampus. Population and single-cell RNA-seq revealed that the subiculum could be divided into two spatially adjacent subregions that exhibited prominent differences in pyramidal cell gene expression. We found that these two regions varied in their long range inputs, local wiring, projection targets, and electrophysiology. Leveraging the gene-expression differences between these regions, we used region-specific neuronal silencing to show that they provide distinct contributions to spatial working memory. This work provides a coherent molecular-, cellular-, circuit-, and behavioral-level illustration that the hippocampus embeds structurally and functionally dissociable streams within its serial architecture.

3-F-112 Can You Teach an Old Neuron New Tricks?

John Darby Cole[1], Delane Espinueva[1], Timothy O'Leary[1], Desiree Seib[1], Jason Snyder[1]

[1]University of British Columbia

While new neurons are continuously added postnatally in the dentate gyrus of the hippocampus, only a fraction survive to integrate into the existing neural circuitry. Hippocampal-dependent learning during early developmental stages of adult-born cells increases their survival and accelerates the functional integration, with lasting positive morphological effects. However, little is understood about the learning-induced morphological plasticity in granule cells across stages of maturity. The present study therefore examined the effects of intensive water maze training on dendritic, axonal, and spine morphology in retroviral labeled granule cells, birth-dated at either post-natal day one, or in adulthood at 1, 3, or 6 weeks prior to testing. At present, our data support the previous findings that 1-week-old cells exposed to learning display morphological traits of more advanced maturity than untrained controls. Following learning, there is also a trend for increased mushroom spine density in the 6-week-old and developmental cell populations. Furthermore, adult-born cells display greater spine density in dendritic segments that receive neocortical inputs, which is not observed in developmental-born cells. Continued analyses of dendritic length and complexity, as well as presynaptic terminal frequency, size, and morphology will further our understanding of the plastic potential of granule cells across stages of maturity. Collectively, our data suggest that the potential for learning-induced plasticity diminishes as cells mature, but is not fully extinguished.

3-F-113 Neural correlates of risk/reward decision making in the medial prefrontal cortex and basolateral amygdala

Einar Einarsson[1], Ryan Fayyazi[1], Jeremy Seamans[1], Stan Floresco[1]

[1]University of British Columbia

Reward processing abnormalities are central to the pathophysiology of several psychiatric disorders, characterized by poor performance on tests of probabilistic decision making involving choices between safe but modest rewards, and uncertain but more rewarding outcomes. The basolateral amygdala (BLA) and medial prefrontal cortex (mPFC) are reciprocally connected regions in a neural circuit that make differential contributions in guiding risk/reward decision making, with the mPFC involved in adjusting behavior in response to the outcomes of previous choices, whereas the BLA supports value representation. However, how neurons in the mPFC and BLA encode different type of information regarding the direction of choice and outcomes during decision making remains poorly understood. Here, we examined firing of mPFC and BLA neurons during key task events (e.g. pre-choice, after rewarded/non-rewarded choice outcomes) during a probabilistic discounting task. To this end, we recorded multi-unit activity simultaneously from both regions using multi-tetrode arrays during performance of a task where rats chose between a small/certain reward and a large risky/one, with reward probabilities changing over blocks of free-choice trials from 70% to 10%. Preliminary observations suggest that neurons in both regions are sensitive to changes in large/risky reward probability and the direction of choice, modifying their activity tonically and phasically to key task events.

3-F-114 Neuroanatomical Correlates of Mouse Home Cage Social Behaviours

Darren Fernandes[1], Lily Qiu[2], Brooke Green[3], Jason Lerch[2]

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

Social behaviour is an important function of the brains of humans and mice. However, the neurological basis of natural and longitudinal social interactions are poorly known. While mouse studies have been useful in understanding this relationship, social behaviour is typically quantified in artificial paradigms over short-timescales. Using a combination of video and Radio Frequency ID (RFID) tracking, we tracked and phenotyped several groups of individually-identifiable mice in standard laboratory housing. RFID data was analyzed using information theory to calculate social and non-social behaviour metrics. Our behavioural measures captured known socialibity differences in the BTBR and C57BL6/J mouse strain. C57BL6/J mice were

monitored simultaneously over several weeks, through the development periods of puberty and early adulthood. In conjunction, Manganese-Enhanced MRI was used to obtain longitudinal in-vivo neuroanatomy over this observation period. We found that the size of cerebellar, hippocampal, and frontal cortical regions are significantly associated with mouse social behaviour. Furthermore, cerebellar and frontal cortical volumes in neonatal life are associated with social behaviour post-puberty. Our sociability measures also correlated with sociability scores from the three-chamber novel sociability paradigm.

3-F-115 Ventro-dorsal hippocampal interaction controls context memory formation

Felipe Fredes[1], Maria Alejandra Silva[1], Kenta Kobayashi[2], Maximilian Joesch[1], Ryuichi Shigemoto[1]

[1]Institute of Science and Technology Austria IST, [2]National Institute for Physiological Sciences

The hippocampus has been shown to be a key structure for the formation and recall of memories. In particular, the activity of dorsal hippocampal dentate granule cells (GCs) has been shown to be crucial for context memory formation. Even though projections from the entorhinal cortex can convey the excitatory activity to dorsal GCs, GCs are unlikely to fire solely by entorhinal inputs. Thus, the mechanism for dorsal GCs activation remains elusive. Here we show that mossy cells (MCs) located in the ventral dentate gyrus exert a powerful excitatory drive over dorsal GCs, and their activity is necessary to excite dorsal GCs during novel environment exploration. Using in vivo calcium imaging in freely behaving mice, we found that ventral MCs and dorsal GCs increase and decrease their activities in a correlative way during novel environment exploration and its familiarization. Furthermore, during the acquisition phase of contextual fear conditioning, inhibition of ventral MCs terminals in the dorsal dentate gyrus robustly reduces freezing during subsequent retrieval. Thus, we propose that the activity of ventral MCs operates as a gating mechanism for dorsal GCs firing. These findings reveal a previously overlooked intra-hippocampal ventro-dorsal interaction that serves a critical mechanism to mediate context memory formation.

3-F-116 Early intervention with a multi-ingredient dietary supplement improves mood and delays spatial memory decline in a triple transgenic mouse model of Alzheimer?s disease

Craig Hutton[1], Jennifer Lemon[1], Boris Sakic[1], David Rollo[1], Douglas Boreham[1], Margaret Fahnestock[1], Martin Wojtowicz[2], Sue Becker[1]

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

The failure of conventional treatments to stop neurodegeneration in Alzheimer's disease (AD) necessitates an alternative approach. Evidence of inflammation, mitochondrial dysfunction, and oxidative stress prior to the accumulation of amyloid-β in the prodromal stage of AD (mild cognitive impairment; MCI) suggests that early interventions which counteract these features, such as dietary supplements, may ameliorate the onset of MCI-like behavioural symptoms. We administered a polyphenol-containing multiple ingredient dietary supplement (MDS), or vehicle, to both sexes of triple transgenic (3xTg-AD) mice and wildtype mice between 2-4 months of age. We hypothesized that the MDS would preserve spatial learning, which is known to be impaired in untreated 3xTg-AD mice by 4 months of age. Behavioural phenotyping of animals was done at 1-2 and 3-4 months of age using a comprehensive battery of tests. As previously reported in males, both sexes of 3xTg-AD mice exhibited increased anxiety-like behaviour at 1-2 months of age, prior to deficits in learning and memory, which did not appear until 3-4 months of age. The MDS did not reduce this anxiety, or prevent impairments in novel object recognition (both sexes) or on the water maze probe trial (females only). Strikingly, the MDS specifically prevented male and female 3xTg-AD mice from developing impairments in working memory and spatial learning. The MDS also increased sucrose preference, an indicator of hedonic tone. These data show that the MDS can delay some, but not all, psychopathology in an AD model.

3-F-117 The Effect of Social Context on Functional Connectivity and Between-Brain Coupling

Amna Hyder[1], Naznin Virji-Babul[1]

[1]University of British Columbia

Human brains are shaped by their interactions with others. Most studies in social neuroscience focus on an individual subject within a constrained social context. However, perceptual and motor actions do not occur in social isolation and little is known about how the activity of one brain dynamically changes as a function of the other during a real social interaction. The aims of this study were to: a) investigate changes in functional connectivity in varying social contexts (cooperative, competitive and independent) between two individuals and b) quantify emergent properties of two brains interacting simultaneously. 48 right handed females (ages: 17-30) came

in as dyads. Each dyad participated in a game which required responding to a green light with a button press under the following conditions: 1) independent: one participant is asked to respond, while the other observes, 2) cooperative: both are asked to synchronize their responses, and 3) competitive: both are asked to respond faster than the other. EEG and behavioural data was collected in each. We applied graph theory analysis on EEG data to evaluate functional connectivity. We found higher clustering in right frontal regions during the cooperative condition, and higher clustering in left frontal regions during the competitive condition. These preliminary results suggest that brain-behaviour relationships are dynamically altered during social interactions & influenced by the nature of the task. Further work is underway to detect the emergent properties and differences in brain-brain synchrony across conditions.

3-F-119 Chronic Traffic Noise Exposure Increases the Risk of Developing Alzheimer's Disease

Hadil Karem[1], Zahra Jafari[1], Majid Mohajerani[1]

[1]University of Lethbridge

Traffic noise has become a daily source of stress in the modern societies. While living next to high traffic roads has shown to be associated with increased risk of developing Alzheimer's disease (AD), a few experimental studies were performed to understand this association. In this study, we employed a combination of behavioral, biochemical, and histological techniques to investigate the impact of a chronic traffic noise paradigm on the development of the AD. The APPNL-G-F mice from both genders were randomly assigned to either the traffic noise exposure group (75 dB SPL, 8 hrs/30days) or control group. The adverse effects of traffic noise stress on corticosterone levels, animals' behavior, and development of amyloid beta (Aβ) plaques were examined at ages 4 and 6 months. The chronic traffic noise exposure significantly exacerbated the development of Aβ plaques, and also caused anxiety-like behavior, reduced learning and memory, and impaired balance and motor coordination in stressed mice compared with the controls. The results provide evidence that chronic traffic noise exposure negatively modifies brain structure-function and accelerates Aβ pathology as a predisposing factor in the development of the AD.

3-F-120 Characterization of a neural circuit in a mouse model of schizophrenia

Benjamin Karimi[1], Shreya Dhume[1], Tabrez Siddiqui[1]

[1]University of Manitoba

Schizophrenia is a debilitating disorder affecting cognition and behaviour. Genome wide association studies (GWAS) have implicated genes encoding for synaptic cell adhesion proteins and the associated signal transduction machinery in schizophrenia. Leucine-rich-repeat transmembrane neuronal protein (LRRTM1) was identified as causative in schizophrenia in a meta-analysis of several GWAS studies. Lrrtm1 localizes to glutamate postsynapses and mediates synapse development through binding to presynaptic neurexins. Lrrtm1 has a region-restricted expression pattern in the brain, with the strongest expression in the hippocampal CA1 subfield and all thalamic nuclei including the mediodorsal nucleus (MD). The MD has reciprocal connections with the prefrontal cortex (PFC). The MD-PFC circuitry has been identified by multiple groups to underlie social behaviour and working memory deficits in schizophrenia. To determine the contribution of Lrrtm1 in synapse development and the MD-PFC associated behaviour, we injected AAV9-CamKII-eGFP-Cre bilaterally to the MD of 6-8 weeks old Lrrtm1 floxed mice. Acute deletion of Lrrtm1 in the MD of adult mice produced behaviour that phenocopied known deficits in schizophrenia: mild anxiety and strong impairments in social interaction and working memory. Additionally, though synapse numbers were unchanged, glutamatergic transmission and network activity in the MD were impaired. These results indicate that Lrrtm1 drives excitatory synaptic transmission in the MD, which is required for normal MD-PFC circuit function.

3-F-121 Does repetitive, intentional heading cause sub-concussive injury in the young adult brain?

Rebecca Kenny[1], Aaron Varga[1], Chantel Mayo[1], Jodie Gawryluk[1], Mauricio Garcia-Barrera[1], Brian Christie[1]

[1]University of Victoria

Heading is an important part of soccer, yet recent research has indicated that cumulative effects of repetitive heading may cause sub-concussive injury (Koerte et al., 2015). The current study aimed to prospectively investigate the effects of repetitive, intentional heading in soccer practice on brain structure and function using a within-subjects design. Participants included 10 soccer players (20.5+/-2.84) that were examined immediately pre and post heading practice. Magnetic

resonance imaging data were acquired on a 3T GE Scanner with diffusion tensor imaging (DTI). Behavioural measures were also completed pre and post soccer heading and included the SCAT-3 and several short computerized tasks that involve executive functions. An accelerometer was used to measure the force of the impact during soccer heading. DTI analyses were completed using FSL's Tract Based Spatial Statistics to examine changes in both fractional anisotropy (FA) and mean diffusivity (MD) due to heading the soccer ball. The current study investigated microstructural changes and behavioural performance in young soccer players. Results indicated heading impacts were not greater than 10g. At this level of impact, there were no significant pre-post heading differences in either FA or MD. Additionally, there was no significant differences in SCAT-3 scores between groups. The current work shows initial evidence that repetitive heading in soccer in a practice setting does not cause structural brain damage. Future analysis will investigate the relationship between the MRI data and the behavioural data.

3-F-122 The effect of chronic glycogen synthase kinase 3β inhibition on the behaviour and neuroanatomy of five mouse models of autism

Zsuzsa Lindenmaier[1], Adrienne Kinman[2], Tiffany Chien[2], Kaitlyn Easson[2], Jacob Ellegood[2], Jane Foster[3], Evdokia Anagnostou[2], Jason Lerch[4]

[1]University of Toronto, [2]Hospital for Sick Children, [3]McMaster University, [4]The Hospital for Sick Children

This study aims to categorize Fmr1, Chd8, Arid1b, Shank3 and Nhs mice into groups based on responsivity to the drug Tideglusib and to characterize the effects of Tideglusib on behaviour and neuroanatomy. Tideglusib, a glycogen synthases kinase β inhibitor, is predicted to alleviate autism-related symptoms, increase neurogenesis and memory formation (Guo et al.2012, Hermida et al. 2017). Mice were administered Tideglusib via I.P. injection five days a week for four weeks beginning when they reached 5 weeks of age. A battery of behavioural assessments were conducted on the final week of treatment to assess sociability, memory, anxiety and hyperactivity. We used magnetic resonance imaging (MRI) scans at three timepoints to assess the effect of treatment on neuroanatomy. We found a significant treatment effect of Tideglusib in two of the strains used. Shank3 mice exhibited a normalized memory deficit, decreased anxiety and exacerbated hyperactivity. Tideglusib treatment in Nhs mice resulted in a decreased level of anxiety. Fmr1, Chd8 and Arid1b mice showed no significant treatment effect. Tideglusib had a significant effect on the behaviour of Shank3 and Nhs mice. Shank3 mice showed significant effects on memory, anxiety and hyperactivity and Nhs mice significant effects on

anxiety. This altered behaviour in Shank3 mice is not necessarily beneficial for patients with autism, given that treatment increased hyperactivity. Overall, both Nhs and Shank3 mice responded to Tideglusib but attention should be paid to the positive and negative effects Tideglusib may have on behaviour.

3-F-123 Prenatal Disruption of D1R-SynGAP Complex Impairs GABAergic Interneuron Migration and Causes Cognitive Deficits in Adulthood

Terence Kai Ying Lai[1], Ping Su[2], Frankie Lee[2], Andrew Abela[2], Paul Fletcher[1], Fang Liu[1]

[1]University of Toronto, [2]Campbell Family Mental Health Research Institute

Background: The dopamine D1 receptor plays a role in GABAergic interneuron migration, but the molecular mechanism underlying such actions remains unclear. Meanwhile, synaptic Ras-GTPase activating protein (SynGAP) also plays a role in the innervation of GABAergic interneurons. In this study, we used co-immunoprecipitation to confirm a protein-protein interaction between D1R and SynGAP, and we aimed to determine whether this disruption possesses any regulatory role in the migration of GABAergic interneurons, as well as in cognitive behaviors. Methods: An interfering peptide was injected into pregnant mice to disrupt the protein complex during neurodevelopment. Immunofluorescent staining was used to analyze the distribution of GABAergic interneurons in the offspring mice. The offspring also underwent a wide range of behavioral assessments. Results: We found that the disruption of the D1R-SynGAP complex led to profound GABAergic interneuron migration deficits. In addition, the administration of the interfering peptide to pregnant mice led to abnormalities in locomotor activity, pre-pulse inhibition, sociability and visual discrimination in the offspring. Conclusions: This study revealed a novel protein-protein interaction between D1R and SynGAP, and also confirmed that this interaction plays an important role in the prenatal GABAergic interneuron migration and the development of important behaviors in adulthood.

3-F-124 Aerobic exercise does not help improve long-term cognitive alterations present in middle to late adulthood mild traumatic brain injury (mTBI) victims

Camille Larson-Dupuis[1], Hélène Bergeron[2], Edith Léveillé[3], Martine Desjardins[3], Véronique Pepin[4], Louis De Beaumont[1]

[1]Université de Montréal, [2]Université du Québec à Trois-Rivières, [3]Montreal Sacred Heart Research Center, [4]Concordia University

Little is known about the long-term impact of sustaining a single mTBI combined to the effects of aging. Also, very few interventions exist to treat mTBI patients and prevent a possible accelerated cognitive decline. This study aims to 1- examine the long-term effects of a single mTBI on cognition, 2- evaluate the cognitive effects of an aerobic exercise program for mTBI patients. Thirty-nine participants aged between 50 and 70 were assessed using various neuropsychological tests. Among them, half had sustained a mTBI 2 to 7 years earlier. Significant differences were found between controls and mTBI patients on tests (Stroop, Verbal Fluency, TOL and BVMT) assessing information processing speed, executive function and visual memory. Sixteen of the mTBI patients then engaged in a 12-week physical exercise program. They were divided into two equal groups - subjected either to aerobic training on cycle ergometers or stretching exercises. The participants' physical condition (VO2max) was evaluated pre- and post-intervention and neuropsychological tests showing significant differences between mTBIs and controls at baseline were re-administered post-intervention. Participants from the aerobic group improved their physical condition significantly more than those from the stretching group. However, no between-group differences were found on neuropsychological measures after the intervention. Results from this study show that a 12-week aerobic exercise program did not lead to cognitive improvements in a limited sample of late adulthood mTBI patients injured 2-7 years earlier.

3-F-125 Depressive behaviour and the dorsal raphe: Sex-specific effects of chronic social isolation

David Oliver[1], Katheron Intson[1], Derya Sargin[1], Evelyn Lambe[1]

[1]University of Toronto

Chronic social isolation is a well-established risk factor in the development of depressive disorders in humans and depressive-like behaviours in rodents. Recent work from our lab has shown that chronic social isolation from weaning into adulthood alters dorsal raphe serotonin neuronal excitability in male mice, as well as leading to a depressive-like behavioural phenotype (Sargin et al., eLife 2016). Here we examine sex differences in behaviour and dorsal raphe serotonin neuronal electrophysiology at baseline and following chronic social isolation. We find increased depressive-like behaviour in group-housed female mice compared to group-housed males on the novelty suppressed feeding test and the forced swim test, but seemingly opposite

effects of social isolation in males and females. Paralleling these differences, we observe sex- and housing-specific differences in the excitability of serotonergic neurons in the dorsal raphe. Following social isolation, male mice show decreases in serotonin neuronal excitability, while female mice show increases. Ongoing experiments are investigating the cellular and molecular mechanisms contributing to these sex-specific effects of chronic social isolation. Since there are prominent sex differences in the incidence and possibly the etiology of mood disorders, it is vital to examine the sex specificity of neurobiological changes in response to risk factors.

3-F-127 Targeted memory reactivation during rapid eye movement sleep improves procedural skills learned in virtual reality: a pilot study

Claudia Picard-Deland[1], Arnaud Samson-Richer[2], Julianne Chénier[2], Tyna Paquette[2], Tore Nielsen[1]

[1]Université de Montréal; Dream and Nightmare Laboratory, Center for Advanced Research in Sleep Medici, [2]Dream and Nightmare Laboratory, Center for Advanced Research in Sleep Medicine, Hôpital du Sacré-Coe

Offline reactivation of newly encoded memories is a central process by which sleep contributes to memory consolidation. While these neural replays occur spontaneously during both rapid eye movement (REM) and non-REM sleep, a growing body of research shows that they can also be triggered by replaying an auditory stimulus that was associated with the initial learning, a method known as targeted memory reactivation (TMR). Our pilot study aims to enhance procedural learning of a VR-flying task with TMR by presenting task-associated tones during REM sleep. A total of 21 subjects (22.9±3.49 yrs old; 14 F) completed the task before and after a polysomnographically-recorded morning nap during which the tones were either replayed (N=10; Stim) or were absent (N=11; control). The task involved flying through a circuit of rings in a natural landscape as precisely and quickly as possible. A mixed-design ANOVA revealed a significant interaction between time (pre-nap, post-nap) and condition (control, Stim), $F(1,21)=5.083$, $p=.036$, with a larger improvement in performance for the Stim group, $t(19)=-3.491$, $p=.002$. These results, although preliminary, suggest that TMR during REM sleep could influence sensorimotor skill performance, presumably by reactivating neural circuits involved in the VR-task learning. Future studies will aim to confirm these results with a larger sample and analyses of more precise sleep micro- and macro-structure measures. Findings may help in the development of new sleep-based methods that use VR to optimize and rehabilitate balance and motor memory.

3-F-128 Assessing the Contribution of Anterior Cingulate Cortex On Checking Behaviors in a Rat Model of Obsessive Compulsive Disorder

Sukriti Gupta[1], Nathaniel Powell[1], Jeremy Seamans[1]

[1]University of British Columbia

Obsessive-compulsive disorder (OCD) is a severe, chronic disorder characterized by intrusive, persistent and uncontrollable thoughts or urges (obsessions), and repetitive behaviors or mental acts executed to avoid distress (compulsions) (Greenberg, Rauch, & Haber, 2010). Most patients receive adequate relief from symptoms through medications, cognitive-behavioral therapy, exposure therapy, and ritual prevention (Garrett et al., 2015). However, in 10-20% of the patients, OCD is refractory to these treatment approaches; in such situations, the patients are candidates for a surgical intervention (Rauch et al., 2001). For these patients a dorsal anterior cingulotomy (lesioning the dorsal Anterior Cingulate Cortex (ACC)) is a common surgical treatment (Garrett et al., 2015). This approach has been shown to be helpful in relieving symptoms (> 35% reduction in the Yale-Brown Obsessive Compulsive Scale) in 40% of the patients (Rauch et al., 2001). Although anterior cingulotomies have shown success in mediating the symptoms of OCD, the role of ACC in this disorder remains unclear. Having a rat model to understand the neural mechanisms of the ACC that contribute in OCD would provide a valuable tool for studying this disorder. Our current project is to create a rat model of checking behaviors that are commonly observed in patients with OCD. We intend to use this model to investigate the role of ACC in these behaviors through inactivation studies and potentially electrophysiological recording. Presently, the rats are learning the task, but here we show early behavioral results.

3-F-129 Functional mapping of cortical dopamine D2 receptor expressing neurons

Clémentine Quintana[1], Jivan Khlghatyan[2], Martin Parent[2], Jean Martin Beaulieu[1]

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

Background: The D2 receptor (Drd2) is a direct or indirect target of antipsychotics and mood stabilizers. Expression and function of Drd2 has mostly been studied in the striatum and prefrontal cortex, considering the involvement of these regions in mental disorders. Limitations of mouse models and technical approaches hindered reliable mapping of Drd2 neurons particularly in cortex. Methods: We used immunohistochemistry, translational profiling, viral

tracing on a RiboTag mouse model, which express HA tagged ribosomal protein specifically in Drd2 expressing cells. Results: We mapped brain wide expression pattern of Drd2 and revealed previously unidentified cortical clusters of Drd2 expressing cells. Cell type specific characterization and translation profiling of Drd2 cells indicate their heterogeneity and proportion in various cortical regions. Furthermore, we demonstrate the modulation of translation profiles of these clusters of Drd2 neurons after chronic antipsychotic treatment, thus highlight the functional activity of D2 receptor. Ultimately we constructed a comprehensive connectomic map that may point to a possible functional role of Drd2 neurons from various regions. Conclusions: This comprehensive map of Drd2 neurons provides indications for its functional implications in healthy and disease conditions, such as schizophrenia and can be used as a resource for future investigations. Multiple Drd2 neuron containing brain regions and cell types have to be taken into consideration during pharmacological intervention and assessment of functional and behavioral data.

3-F-130 Functional connectivity organization underlying emotion perception in 8 month old infants following prenatal maternal exposure to SSRIs - Preliminary results

Naama Rotem-Kohavi[1], Naznin Virji-Babul[1], Tim Oberlander[1]

[1]University of British Columbia

Emotion perception is critical for developing social interaction in infancy. Mother's mood during and following pregnancy has been associated with long term effects on infant's emotional development. Selective Serotonin Reuptake Inhibitors (SSRIs) commonly used to treat depression during pregnancy have also been associated with infant's behavior and emotional development risks. We have previously shown the functional brain organization in typically developing infants while viewing emotional faces, using graph theory analysis (GTA) applied to electroencephalography (EEG) data. In this study, we took a similar approach to test the functional organization for viewing emotional faces in 8 month old infants prenatally SSRI exposed (n=9) and non-exposed (n=16) infants. We recorded EEG brain responses while infants observed dynamic sad and happy faces and applied GTA to model the brain's functional organization differences between groups. To control for maternal mood we used Edinburgh Postnatal Depression Scale (EPDS) scores during the third trimester, and Beck Depression, positive and negative affect schedule at 8 months as covariates in the analysis. We found an exposure x emotion interaction (p=0.04 mixed ANOVA) stemming from higher global modularity - reflecting higher stability of sub-networks within the global network for viewing

sad faces among prenatally SSRI exposed compared to non-exposed infants (p=0.02). These results suggest that prenatal SSRI exposure might be associated with alterations in functional organization related to viewing sad faces early in infancy

3-F-131 The effect of ketamine on 3D spatial working memory in rhesus macaques

Megan Roussy[1], Rogelio Luna[2], Lena Palaniyappan[1], Julio Martinez-Trujillo[2]

[1]University of Western Ontario, [2]Robarts Research Institute

Ketamine, an NMDA receptor antagonist, causes working memory deficits. Coding of working memory relies on cortical microcircuits composed of various cell types, with lateral prefrontal cortex circuits playing a prominent role. Although NMDA receptors are evidenced to play an important role in prefrontal cortex function, the effect of systemic NMDA antagonists on the responses of prefrontal neurons during working memory remains poorly understood. The current project aims to measure behavioral deficits in working memory after administration of systemic Ketamine and to isolate the effect of NMDA receptor dysfunction on neural encoding of working memory. Two rhesus macaques were implanted with two multi-electrode arrays in prefrontal area 8A. Behavioral performance was examined using a 3D task in which a target appears in a particular spatial location on a virtual arena. After the target disappears, animals must hold the target location in memory during a delay period before navigating to the cued location. We recorded task performance before and after administration of subanesthetic doses of Ketamine. We found that performance significantly deteriorated after Ketamine injection and recovered after 30 minutes. Performance remained stable after control saline injections. Performance also did not change for a perception control task after Ketamine injection. Preliminary analysis of neural data suggests that Ketamine-induced blockade of NMDA receptors decrease the fidelity of working memory representations thus leading to the previously described behavioral effects.

3-F-132 Social communication of stress

Toni-Lee Sterley[1], Jaideep Bains[2]

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

Experiencing a stressful event triggers long-term changes in the brain that mediate changes in behaviour. Recent work from our lab shows that stress can be transmitted from a stressed mouse to one that is naïve, and that this transmitted stress can have similar synaptic implications as the original stress. This transmission requires social interaction that includes social contact, and involves the release and detection of a chemical alarm signal. In the present study we further investigate the communication of stress between mice and ask whether there is a 'behavioural language' involved. We use newly developed analysis software to record spontaneous behaviour of a pair of mice in the homecage after one from the pair experienced a stress. We find that on return to the homecage the stressed mouse displays a specific behavioural motif, including extensive running, rearing, and grooming behaviours. Partner mice, in turn, display highly predictable behaviours including extensive investigation of the stressed mouse. These behaviours are absent on return of an unstressed mouse to the cage. Using these behavioural motifs as a platform for understanding social communication, we can begin exploring questions that will provide insights into how familiarity, prior experience, or social hierarchy affect social transmission of stress or threat signals.

3-F-133 Underperformance in the Workplace: Using a Rodent Model to Explore the Neural Mechanisms of Lost Productivity

Jason Tabor[1], Yannick Griep[1], Richelle Mychasiuk[1]

[1]University of Calgary

Broken promises from employers have been shown to decrease performance on future tasks or result in corporate time-theft, both incurring massive costs in lost productivity. Using a rodent model, we sought to examine the neurological correlates of this behaviour to help explain why employees may conduct themselves this way. 16 male, P60, Sprague Dawley rats were trained in a 5-choice serial reaction test where they received a reward for nose-poking the proper Go stimulus (1/3 possible holes lighting up). Once the animals learned the task, half kept receiving their rewards, Promise Kept (PK), and half no longer received a reward for their work, Promise Broken (PB). Performance efficiencies measured before and after the promise was broken showed the PB group being less efficient after learning they were no longer rewarded for completing the task. Behavioural tests were done to examine locomotion, anxiety, and aggression/dominance levels. Differences were seen in locomotor activity between the two groups, along with increases in aggression and dominance in the PB rats vs. PK cage-mates. When facing a same group cage-mate, rats with a higher efficiency before the promise was

broken were more dominant. Analysis of serum biomarkers showed the PB group to have higher serum testosterone levels than the PK group at the time of sacrifice. qPCR gene expression analysis of the prefrontal cortex (PFC), nucleus accumbens (NAc) and hippocampus (HPC) showed that the NAc was influenced to a greater extent than the PFC or HPC with significant changes in 4 genes (Drd1, GR, Iba1, Maoa).

3-F-134 The Impact of Acute Stress on Visual Processing of Emotional Facial Expressions: An Eye Tracking Study

Shruti Vyas[1], Carson Pun[1], Alexandra Fiocco[1]

[1]Ryerson University

Recognizing basic emotional expressions in social environments is an adaptive ability. Encoding emotional nonverbal facial cues facilitates communication and social interaction. However, past research suggests that acute stress may impact the perception of emotional expressions, such as enhancing recognition of fear and anger. Given these findings, it is important to understand how stress influences visual processing of emotional facial expressions. A total of 53 young adults (M =19.83 years, SD = 3.18) were randomized into a non-stress control group or a stress induction group in which participants underwent the Paced Auditory Serial Addition Task. Both groups completed an emotion recognition task during which eye gaze was tracked with the Eye Link 1000 (SR Research). Eye gaze analysis was conducted using average dwell time (DT) on four regions of interest (eyes, lips, nasion, and nose). A subgroup analysis by group found significant correlations between experimental condition and DT for the nasion and the nose. A Mann-Whitney U Test resulted in significant group differences in DT on the nose for all emotions ($p<0.05$), except fear and happy. On average, participants in the stress group spent less time looking at the nose compared to the control group. A Chi Square Test of Association indicated that participants in the stress group fixated on the nasion significantly more than those in the control group for all emotions ($p<0.05$), except for fear. These findings will be discussed in relation to recognition accuracy of emotional facial expressions following stress exposure.

3-G-136 Highly sensitive and specific in situ detection of splice junctions to visualize expression dynamics in circular RNAs and their linear counterparts at single-cell level in developing mouse brain using BaseScopeTM technology.

Annelies Laeremans[1], Jonathan Samson[1], Emily Park[1], Xiao-Jun Ma[1]

[1]Advanced Cell Diagnostics

Circular RNAs (circRNAs) are very stable single-stranded RNA molecules generated by the alternative splicing and covalent linkage of the 5' end of one exon with the 3' end of another exon. These highly conserved circRNAs are developmentally regulated, and have cell-type and tissue specific expression patterns with a particular abundance in the brain. While some circRNAs have been shown to function as miRNA sponges, for the vast majority of circRNAs their function remains elusive. Recent evidence has emerged that associates varying circRNA expression levels with disease, including cancer and neurological disorders, suggesting circRNAs might be harnessed for diagnosis and treatment. The accurate detection and anatomical localization of circRNAs is pivotal to elucidate their biological function. Here, we used the BaseScopeTM in situ hybridization (ISH) technology to visualize and quantify the expression of circRNAs and their linear mRNA counterparts for Dlgap1 and Klhl2 in P1, P10 and P30 C57Bl/6J mouse brains by detecting splice junctions specific for either circRNA or mRNA. Both genes showed increased circRNA expression over development with prominent changes around the time of synapse formation P10. Also, expression dynamics for circRNAs and mRNAs were independent. Combination with IHC for MAP2 allowed further detail on subcellular localization of these circRNAs. This single-cell ISH assay allows for the highly specific and sensitive visualization of splice junctions characteristic for circular and linear RNA transcripts within the morphological tissue context.

3-G-137 Ultra-fast scanning two-photon microscopy reveals neuronal calcium dynamics in vivo

Tristan Dellazizzo Toth[1], Kelly Sakaki[1], Kasper Podgorski[2], Kurt Haas[1]

[1]University of British Columbia, [2]Janelia Research Campus

Comprehensive imaging of single neuron calcium activity in vivo requires extremely fast imaging rates of three dimensional structures. We have designed a custom two-photon laser scanning microscope (TPLSM) that employs acousto-optic devices that enables us to scan the complete dendritic arbor of a neuron in an awake, unanesthetized brain through the use of random access sampling at substantially increased rates compared to conventional microscopes. Through leveraging the ultra-fast scanning capabilities of this revolutionary microscope in conjunction with the use of a high-affinity genetically encoded calcium indicator (GECI) we are able to record

and analyze calcium dynamics within an entire neuron in a live and intact animal with unprecedented spatial and temporal resolution. We are currently using these to tools to provide us with novel insights examining how neurons process and integrate information.

3-G-138 Common spatial pattern approach to EEG neurofeedback in Parkinson's disease

Emma Kiss[1], Christina Jones[1], Saurabh Garg[1], Soojin Lee[1], Martin McKeown[1]

[1]University of British Columbia

Electroencephalographic (EEG)-based neurofeedback may be an inexpensive, non-invasive treatment strategy for Parkinson's disease (PD). PD may be well-suited for EEG neurofeedback therapy as pathological oscillations are well documented in PD and related to motor symptoms. This pilot study aims to test 3 neurofeedback strategies as a means of modulating EEG in PD. EEG data were recorded from 4 PD participants on medication using a lightweight, dry, wireless, 6-electrode headband (Cognionics, USA). After instruction, participants performed three modulation strategies (3x 60s trials each) in randomized order: imagining movement, imagining rewards, and mindfulness meditation. A common spatial pattern (CSP) algorithm was used on a subject-by-subject basis to maximize variance during modulation strategies compared to rest. Average power was calculated for each strategy across 5 EEG bands. The EEG could be effectively modulated in all PD subjects, but the strategies had differing effects across subjects. Trial-by-trial variability was substantially lower with the CSP combination of electrodes compared to any individual channel ($p < 0.0001$). Our results suggest 1) PD subjects are able to effectively manipulate the EEG (measurable by consumer quality EEG headsets) and 2) CSP is a reasonable preprocessing strategy for EEG based neurofeedback. Further work is required to determine optimal strategies for EEG neurofeedback, if PD subjects can use this newfound capacity to modulate their EEG to "normalize" their EEG, and if EEG normalization translates into behavioural improvement.

3-G-139 Decoding cortical and subcortical spike activity from mesoscopic cortex-wide calcium dynamics

Anna Luo[1], Dongsheng Xiao[1], Timothy Murphy[1]

[1]University of British Columbia

The cerebral cortex is connected to subcortical structures through multiple descending and ascending pathways. Mesoscopic cortex-wide dynamics may embed spatiotemporal patterns that reflect and contribute to subcortical neural activity. We simultaneously recorded wide-field GCaMP imaging and multi-unit spike trains in mice. To discover spike-predictive patterns in GCaMP, we trained fully-connected neural networks to discriminate GCaMP sequences spanning 500msec around a spike (positive examples) or a quiescent period (negative examples). The average gradients from the neural networks for positive test examples formed the cortical feature map. Instantaneous activation of the cortical feature map in the GCaMP data was used to predict instantaneous firing rate via a generalized linear model. For cortical (barrel cortex, N=16 units) spike activity, predicted firing rates accounted for 29.26% (±11.80%) of the variance in the spike trains, and the cortical feature maps emphasized dynamics in the barrel and primary motor cortices after spike onset. For subcortical areas (the thalamus, striatum, or hippocampus, N=48) which connected to the cortex less directly, the predicted variance reduced to 5.61% (±4.64%). Distinct cortical feature maps were found for neighboring multi-units in the same anatomical region, suggesting heterogeneity in cortico-subcortical connectivity for these ensembles. Our findings demonstrate that mesoscopic cortical dynamics contains sufficient information for distinguishing neuronal firing patterns in cortical and, to a lesser extent, subcortical areas.

3-G-140 Machine Learning Based Responsive Brain Stimulation: An Epilepsy Clinical Trial

Gerard O'Leary[1], David Groppe[1], Taufik valiante[1], Roman Genov[1]

[1]University of Toronto

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 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.

3-G-141 Effects of Low Field Magnetic Stimulation on cognitive and motor functions in a Traumatic Brain Injury Mouse Model

Sathiya Sekar[1], Yanbo Zhang[1], Changiz Taghibiglou[1]

[1]University of Saskatchewan

Traumatic brain injury/concussion (TBI) is a growing epidemic throughout the world. Memory and neurobehavioral dysfunctions are among the sequelae of TBI. TBI has been increasingly accepted as one of the major external risk factor in the development/progression of neurodegenerative diseases. Low-field magnetic stimulation (LFMS) is a new non-invasive transcranial magnetic stimulation (TMS) technique that generates deep brain magnetic stimulation. In the present study, the potential therapeutic effects of LFMS on cognitive and motor functions were investigated in a weight drop induced TBI mouse model. LFMS treated TBI mice covered longer distance in open field when compared to vehicle treated TBI mice. In addition, they moved center squares like normal control and LFMS control mice, whilst vehicle treated TBI mice spent less time in the center squares of open field. Further, LFMS treated TBI mice withstand more time on the rotating rod, whilst vehicle treated mice fall in short time compared to normal control mice. In novel location task, LFMS treated mice spent more time in the novel location compared to vehicle treated mice. In our preliminary study, we reported the release of cellular prion protein (PrPc), a lipid raft protein from brain to circulation following sport concussion and blast-induced brain injury. Here, we observed increased PrPc levels in LFMS treated mice brain compared to vehicle treated which shows the restorative effect of LFMS. Thus, the results obtained from the study suggest that LFMS may be a potentially therapeutic choice for the treatment of TBI.

3-G-142 Strategies Towards Live Imaging for 3D Glial Cell Cultures: A Preliminary Study

Christopher Tsui[1], Kyle Koss[1], Matthew Churchward[1], Mischa Bandet[1], Ian Winship[1], Kathryn Todd[1]

[1]University of Alberta

In the central nervous system, damage resulting from events such as stroke, traumatic brain injury, or implantation of electrodes or other biomaterials will typically elicit a sustained inflammatory response that includes gliosis, cell death, and glial scar formation that can exacerbate injury and prevent healthy recovery of affected tissue. We make use of photocrosslinked methacrylated hyaluronic acid (HAMA) hydrogels which are a reproducible means of housing primary glial cells (microglia, astrocytes, oligodendrocytes) and evaluating their reactivity in a 3-dimensional in vitro environment in response to different injuries. It is thus of interest to observe glial cell behaviour through the entire thickness of a HAMA hydrogel in response to a given injury through live, deep imaging. Here, we explore strategies useful for live imaging by comparing different fluorescent imaging modalities - confocal microscopy and two-photon microscopy - in terms of depth resolution on fixed, immunolabelled gels. When paired with non-descanned detection, two-photon microscopy resolved more features at greater depths compared to confocal microscopy. In order to track live fluorescent cells, the feasibility of imaging primary glial cells transfected with green fluorescent protein (GFP) or labelled with fluorescent vital dyes was also investigated. These approaches highlight the utility and versatility of a 3D in vitro culture approach for study of neuroinflammation.

3-G-143 Two-colour optogenetics for studying the roles of cAMP and cGMP in target synapses and subregions of the brain

Megan Valencia[1], Thomas Luyben[1], Kenichi Okamoto[2]

[1]University of Toronto, [2]Lunenfeld-Tanenbaum Research Institute

Intracellular messengers cAMP and cGMP are thought to invoke synaptic plasticity and contribute to learning/memory and disease. However, their signalling dynamics and interactions at synapses remain elusive because conventional approaches have limited cellular precision and spatiotemporal specificity. Here we report novel two-colour optogenetic approaches for selectively activating cAMP and cGMP signalling by light in living neurons. To directly examine the interactive roles of cAMP and cGMP, we utilized the combination of blue light-sensitive adenylyl cyclase (PAC) and green light-sensitive rhodopsin guanylyl cyclase (RhGC). We measured their enzymatic activities with different colors of light and determined distinct

excitation wavelengths for independent cAMP and cGMP synthesis. We coexpressed the enzymes in the hippocampal dentate gyrus (DG) granule neurons of the mouse brain and validated their photoactivation. Furthermore, we characterized the two-photon excitation spectrum of the enzymes and optimized a combination of two-photon excitation wavelengths for independent photoactivation of PAC and RhGC. We applied this approach to selectively manipulate the levels of cAMP and cGMP at target dendritic spines of CA1 pyramidal neurons and demonstrated their function in the rapid and bidirectional regulation of structural synaptic plasticity. Thus, our established two-colour optogenetic approach provides powerful tools to directly study spatiotemporal cAMP/cGMP functions in an unprecedented way.

3-G-144 Assessing cognitive and motor behaviours within the mouse home-cage: applications for the study of genetic models of disease

Cameron Woodard[1], Jamie Boyd[1], Timothy Murphy[1], Lynn Raymond[1]

[1]University of British Columbia

Behavioural testing of genetically modified mice is an important step in determining the face and predictive validity of these models. To improve both the throughput and reproducibility of mouse behavioural studies, there has been an increase in the use of automated testing systems that allow for phenotyping of mice within their own home-cage. These allow for the 24-hour testing and monitoring of group-housed mice, who are differentiated through the use of subcutaneously implanted RFID chips. However, current commercially available systems are expensive and limited in their ability to test certain behaviours relevant to the study of neurodegenerative disorders, such as motor skill learning. To address this, we have developed an open-source system to assess motor learning, reversal learning and kinematic measures of forelimb motor control within the mouse home-cage. In previous work with an early version of this system, we found several motor learning and control deficits in the YAC128 model of Huntington disease (HD). Current work has focused on refining the testing methodology and hardware of the system, and the development of new software applications. Additionally, we continue to assess both the YAC128 and Q175FDN models of HD for motor, cognitive and circadian phenotypes, and to characterize progression over time. This platform should prove useful for preclinical drug trials toward improved treatments in HD and other neurodegenerative disorders. Supported by the Canadian Institutes of Health Research grant FDN-143210 to LAR and the Huntington Society of Canada.

3-G-145 Using 3D cell-printing to study astrocytes morphology changes in real time

Mitra Tabatabaee[1], Kabilan Sakthivel[1], Keekyoung Kim[1], Frederic Menard[1]

[1]University of British Columbia Okanagan

Astrocytes are known to play a key role in synapse formation. They ensheath and maintain neural synapses by extending their fine processes. However, how astrocytes initiate such cellular ramifications--and when--remains an enigma. The expression of L-type voltage gated calcium channels (LVGCCs) in astrocytes suggests a plausible mechanism of directional sensing that would control astrocytic protrusions. In contrast to other voltage-gated ion channels, LVGCCs possess conserved chemotactic receptors motifs, which, combined to their known interaction with actin cytoskeleton, support a role in controlling the motility of astrocytes' processes. Typical 2D cell culture in dishes is not appropriate to study the morphological changes of astrocytes in physiologic conditions. Thus, we have developed a biocompatible 3D matrix with a gelatin-based hydrogel that allows us to bio-print with high spatial control. Within this 3D structure, astrocytes retain the morphology that they have in brain tissue. Live actin staining allows the quantification of fine astrocytic processes movement upon stimuli. In addition, we can visualize the dynamics of LVGCCs in living cells with a molecular fluorescent imaging probe (prepared in house), along with calcium flux dyes. Together, these techniques reveal that astrocytic processes protrusion is triggered upon external neurotransmitter release. These responses are also sensitive to blockers of LVGCCs' subunits. Our early results open the possibility of studying multi-cellular responses in vitro while retaining the cells' viability and natural functions

3-H-146 A Brain Museum Tour of Europe

Richard Brown[1]

[1]Dalhousie University

Europe has a rich history of neuroscience, but where can the history of European neuroscience be found? The historical artifacts, documents and discoveries of European neuroscience exist in many museums, but these are often forgotten or neglected within Europe and relatively unknown outside of Europe. The purpose of this project is to present a tour of the brain museums of Europe on a WEBSITE, showing the museums with materials relevant to the history of neuroscience in each country. The history of neuroscience relies of objects from the past and this website describes the collections related to brain research in European museums. Using this

website will enable students and researchers to locate historical objects in museums and plan visits to these museums for teaching and research. The presentation will consist of a short lecture on the project, a poster presentation and a website which meeting participants can browse for information. The present Website contains information on 31 brain museums in 18 countries, with more being added as we find them. The website is a work in progress and we hope that users will provide us with information about brain museums which we have not yet discovered. If you are planning a trip to one of the European cities with a brain museum, this website will guide you to the location and the exhibitions on view. Enjoy your tour of Brain Museums in Europe! This project is sponsored by the FENS History of Neuroscience Committee. If you know of brain museums not presented here, please contact Richard Brown at rebrown@dal.ca.

3-IBRO-147 The exercise-induced hormone FNDC5/irisin contributes to hippocampal function and synaptic plasticity in adult mice

Luis Eduardo Bettio[1], Michael Young[2], Cristina Pinar[1], Waisley Yang[1], Mohammad Islam[2], Christiane Wrann[2], Brian Christie[1]

[1]University of Victoria, [2]Harvard Medical School

Fibronectin type III domain-containing protein 5 (FNDC5) is a transmembrane protein that undergoes proteolytic processing to generate irisin, a soluble hormone that is secreted into the bloodstream. FNDC5/irisin was recently identified as a myokine upregulated after endurance exercise that mediates some of the major metabolic benefits induced by this intervention. This increased expression of FNDC5 induced by exercise was also found in the hippocampus, a structure critical for neuroplasticity in the adult brain. Given that FNDC5/irisin has been implicated in the regulation of BDNF expression, it is likely that this protein contributes to the beneficial effects that physical exercise exerts on hippocampal function (i.e. cognitive and affective processes). Thus, the present study investigated whether adult mice that lack FNDC5 have impaired cognitive function and synaptic plasticity. We found that animals from both genotypes ran equivalent distances, but that the FNDC5 knockout mice did not show improvements in spatial learning and memory usually induced by running exercise in the Morris Water Maze. In addition, we found that these deficits in learning and memory were associated with a significant reduction in the ability of the FNDC5 knockout animals to maintain long-term potentiation (LTP). Our findings indicate that FNDC5/irisin is a major mediator of the effects of exercise on hippocampal neuroplasticity and cognition.

3-IBRO-148 The effects of repetitive stress on tat protein-induced pro-inflammatory cytokine release and steroid receptor expression in the hippocampus of rats

Khayelihle Makhathini[1], Oualid Abboussi[1], Musa Mabandla[1], William Daniels[2]

[1]University of KwaZulu-Natal, [2]University of Witwatersrand

Human immunodeficiency virus types 1 Tat protein is one of the viral proteins that have been linked to the neurotoxic effects of HIV. Since many individuals living with HIV do so under significant adverse circumstances, the present study investigated whether exposure to stressful conditions would exacerbate harmful effects of tat protein on brain function. Tat protein (10µg/10µl) was injected bilaterally into the dorsal hippocampus of the animal using stereotaxic techniques. The control group received an injection of saline (10µl). Some control and tat protein-treated animals were subjected to restraint stress for 6 hours per day for 28 days and compared to a non-stress group. All animals underwent two behavioural tests, the open field test and the novel object recognition test. Rats treated with tat protein showed the following behavioural changes when compared to control animals: there was a significant decrease in time spent in the centre of the open field during the OFT, a significant reduction in time spent with the novel object during the NORT, but no change in locomotor activity. Real-time PCR data showed that the expression levels of GR and MR mRNA were significantly reduced, while Western blot analysis showed that the protein expression levels of TNF-α and IL-1β were significantly increased. The present findings indicated that injection of tat protein into the hippocampus of rats may lead to anxiety-like behaviour and deficits in learning and memory. Subjecting Tat-treated animals to stress evoked only a modest effect on their behaviour and neurochemistry.

3-IBRO-149 Neuronal expression of NUsc1, a single-chain variable fragment antibody against Aβ oligomers, protects synapses and rescues memory in Alzheimer´s disease models

Maria Clara Selles[1], Magali Cercato[2], Juliana Fortuna[1], Andre Bitencourt[3], Amanda Souza[1], Helena Janickova[4], Maria Baez[2], Jorge de Souza[5], Soniza Alves-Leon[5], Vania Prado[4], Marco Prado[4], Alberto Epstein[6], Anna Salvetti[7], William Klein[8], Ottavio Arancio[9],

[1]Institute of Medical Biochemistry Leopoldo de Meis, Federal University of Rio de Janeiro, [2]Laboratorio de Neuroplasticidad y Neurotoxinas, Instituto de Biología Celular y Neurociencia, Univer, [3]Department of Biochemistry and Immunology, Ribeirao Preto Me

Alzheimer's disease (AD) is the main cause of dementia in the elderly and is characterized by abnormal accumulation of the amyloid-β peptide (Aβ) in the brain. Considerable evidence implicates soluble Aβ oligomers (AβOs) in synapse dysfunction and memory loss in AD. Here, we have investigated the neuroprotection conferred by exogenous and by neuronal expressed NUsc1, a single-chain variable fragment (scFv) antibody that specifically targets AβOs, with low reactivities against Aβ monomers and fibrils. Purified recombinant NUsc1 was found to prevent AβO-induced inhibition of synaptic plasticity in hippocampal slices and block memory impairment in mice that received an intracerebroventricular (i.c.v.) infusion of AβOs. Sustained neuronal expression of NUsc1 was achieved using an adenoassociated virus-derived vector (AAV-NUsc1). AAV-mediated NUsc1 expression significantly reduced AβO binding to hippocampal neurons in culture, and prevented AβO-induced loss of dendritic spines. In vivo, AAV-NUsc1 induced brain expression and secretion of NUsc1, and rescued memory in aged APPswe/PS1ΔE9 AD model mice and in wild type mice that received an i.c.v. infusion of AβOs. Finally, AAV-NUsc1 was found to be capable of inducing NUsc1 expression in adult human brain slice cultures. Results suggest that AAV-NUsc1 may represent a potential tool for gene therapy aimed at preventing synapse damage and memory defects in AD.

3-IBRO-150 Next-generation sequencing and proteomics to identify molecular regulators of regeneration after an injury of the central nervous system in the axolotl

Alonso Ortega-Gurrola[1], Brianda López-Aviña[2], Jesús Chimal-Monroy[2], Iván Velasco-Velázquez[1]

[1]Institute of Cellular Physiology, UNAM, [2]Institute of Biomedical Research, UNAM

The axolotl has emerged as an excellent model for regeneration studies: these animals are able to regenerate a plethora of tissues after an injury, including the Central Nervous System. Here we try to unveil the molecular factors and mechanisms underlying the regeneration of the axolotl´s CNS and characterizing this phenomenon using next-generation sequencing and in silico analysis. We inflicted a mechanical damage to the dorsal pallium of the axolotl brain by taking out a piece of tissue. After injury, we permitted animals to recover and found that regeneration was complete at 40 days post-surgery. We characterized several morphological stages and hallmarks during regeneration through immunofluorescence assays and histological stains; we also analyzed the effect of severing the olfactory nerve on brain regeneration. We

found that in the process of regeneration of the axolotl brain, the wound was completely closed by day 40 post-injury. However, we noticed that the brain was healed at day 20 post-injury; proliferation occurs rapidly from day 14 to day 17 after injury. We also noticed some similarities with the normal pattern of the mammalian telencephalon. Once the stages of regeneration are well characterized, the next approach will be to identify molecular factors that play critical roles in regeneration through RNA-Seq. Total RNA will be isolated and sequenced for mRNA and microRNA expression profiles. Bioinformatic approaches will be performed in order to have an in silico background for subsequent experimental procedures. A proteomics approach is also contemplated.

3-IBRO-151 Myenteric and mucosal enteric glia alterations associated to colonic inflammation in mouse model of Parkinson's disease induced by 6-OHDA

Beatriz Thomasi[1], Luisa Valdetaro[1], Amanda Mussauer[1], Ana Carolina Fernandes[1], Claudio Alberto Serfaty[1], Paula Campello[1], Adriana Melibeu[1], Manuel Gustavo Ribeiro[1], Vivaldo Moura-Neto[2], Ana Lucia Tavares Gomes[3]

[1]Federal Fluminense University, [2]Federal University of Rio de Janeiro, [3]Fluminense Federal University

Parkinson's disease (PD) is nowadays recognized as a gastrointestinal disease with the involvement and dysfunction of the enteric nervous system (ENS). Our aim was to study the state of colonic SNE in the animal model of PD induced by 6-hydroxydopamine (6-OHDA). C57Bl6 mice were subjected to striatal administration of 6-OHDA for induction of the PD model and they had survival times of 1, 2 and 4 weeks (4w) together with a control group. The large intestine (colon) of the animals was removed and processed to be used in different techniques to study IBA1 (macrophage marker) and GFAP (glial marker) proteins. The colonic tissue of animals subjected to 6-OHDA model of PD presented inflammatory infiltrate and a tissue disruption with loss of cytoarchitecture. Through immunofluorescence, we observed an increased IBA1 and GFAP expression during the first weeks in the mucosal layer in the animal model. Also, animals showed an increase in GFAP expression in the neuromuscular layer in the colon one week after induction of the model. The same result could be seen in 4w post model induction. Therefore, the colonic tissue from the animal model of PD showed an expressive alteration of the mucosal layer and increased macrophage population associated with alterations in GFAP in both mucosal and neuromuscular intestinal areas. Increase in GFAP levels is associated with glial reactivity and/or glial proliferation. It is possible that the reactive glia

interactions established with immune cells contribute to inflammatory responses in the pathologic scenario observed in this PD animal model.