SOUTHERN ONTARIO NEUROSCIENCE ASSOCIATION

39th Annual Meeting Program and Abstracts

University of Windsor, May 2nd-3rd, 2019

Abstracts of the 39th Annual Meeting of the Southern Ontario Neuroscience Association, Volume 39, May 2019

SONA2019

General information

The Southern Ontario Neuroscience Association (SONA) was founded in 1980. The membership includes all those interested in neuroscience research from molecular and cellular neuroscience, through invertebrate neurobiology to mammalian and human brain and behaviour. The purpose of the Association is to (1) advance our understanding of the structure and function of the nervous system, (2) bring together neuroscience researchers, both faculty and students from nearby universities, (3) provide opportunity for promotion of neuroscience education, (4) and to provide an opportunity for social contacts among researchers and their students. Our annual meeting is made possible through the support of host institution, external sponsors, and organizers. Special thanks to Prof. Paul Mallet (Department of Psychology, Wilfrid Laurier University) for his help organizing the meeting.

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SONA 2019 Program

May 2, 2019 (Human Kinetics Building)

6:00-7:00 pm **Public Lecture (Room 140)**
Dr. Christopher Abeare (University of Windsor)
Sport-related Concussion

May 3, 2019 (Centre for Engineering Innovation)

8:00-9:00 am **Registration and Breakfast (Outside Room 1100)**

9:00-9:10 am **Opening Remarks (Room 1100)**
Professor Jeff Berryman (Provost, University of Windsor)

9:10-10:50 am **Faculty Speaker Session (Room 1100, Chair: Dr. Huiming Zhang)**

- 9:10-9:35 am **Dr. Robert Bonin (University of Toronto)**
  Plasticity of Pleasure and Pain
- 9:35-10:00 am **Dr. Jeffrey Dason (University of Windsor)**
  A cGMP-dependent protein kinase regulates a nociceptive-like escape behaviour through a plastic sensory circuit
- 10:00-10:25 am **Dr. Anne Simon (Western University)**
  Towards an understanding of the neurocircuitry underlying social spacing in Drosophila melanogaster
- 10:25-10:50 am **Dr. Iva Zovkic (University of Toronto Mississauga)**
  The role of distinct H2A variants in learning and memory

10:50 am-12:20 pm **Poster Session 1 and Coffee Break (Atrium)**

12:20-1:20 pm **Lunch (Atrium) and SONA Councillors Meeting (Room 2103)**

1:20-2:20 pm **Trainee Speaker Session (Room 1100, Chair: Dr. Jeffrey Dason)**

- 1:20-1:35 pm **Radu Gugustea (Western University)**
  Effect of ATRX neuronal inactivation on hippocampal synaptic plasticity in mice
- 1:35-1:50 pm **Roger Hudson (Western University)**
  Delta-9-tetrahydrocannabinol engenders cognitive defects and dysregulates prefrontal cortical single-unit and oscillatory activity via hippocampal mitogen activated protein kinase stimulation

1:50-2:05 pm **Ashutosh Patel (University of Guelph)**
Neuronal responses to muscarinic receptor activation change during postnatal maturation of the medial prefrontal cortex

2:05-2:20 pm **Laura Smithson (University of Michigan)**
Intact synaptic signaling restrains Wnd/DLK-mediated axonal injury response

2:20-3:50 pm **Poster Session 2 and Coffee Break (Atrium)**

3:50-4:50 pm **Keynote Speaker Session (Room 1100, Introduced by Dr. Barbara Zielinski)**
Dr. Michael Salter (SickKids Research Institute)
Cells, Genes, Sex and Mechanisms in Pain

4:50-5:00 pm **Awards (Dr. Dennis Higgs)**

5:00 pm **Closing Remarks (Dr. Huiming Zhang)**

5:00-9:00 pm **Social at Jimmy G's Bar and Grill (2109 Wyandotte St W)**

Note: Posters with odd numbers are to be presented in poster session 1, while posters with even numbers are to be presented in poster session 2.

39th Southern Ontario Neuroscience Association Annual Meeting Abstracts

Faculty Speaker Abstracts

Keynote Speaker, Michael W. Salter, SickKids Research Institute, Toronto, Ontario

Cells, Genes, Sex and Mechanisms in Pain

Neuron-microglial interactions are increasingly recognized as being key for physiological and pathological processes in the central nervous system. Microglia have been found to play a causal role in neuropathic pain behaviours resulting from peripheral nerve injury, and a core neuron-microglia-neuron signaling pathway has been elucidated. Within the dorsal horn, microglia suppress neuronal inhibition by a cascade involving activation of microglial P2X4 receptors causing the release of brain derived neurotrophic factor (BDNF). BDNF acts on trkB receptors which leads to a rise in intracellular Cl^- concentration in dorsal horn nociceptive output neurons, transforming the response properties of these neurons. In addition to suppressing inhibition, peripheral nerve injury causes activity-dependent potentiation at dorsal horn glutamatergic synapses which enhances nociceptive transmission. BDNF mediates the enhancement of synaptic NMDAR responses through activation of TrkB and the Src-family kinase, Fyn. We have discovered that microglia-to-neuron signaling is not only critical for pain hypersensitivity after nerve injury but also for the paradoxical hyperalgesic effect of morphine and other opioids. This core signaling pathway has been extensively characterized, in studies using male mice. We have recently discovered that microglia-neuron signaling is dispensable in female mice. Rather, pain hypersensitivity in female mice depends upon the adaptive immune system, likely upon T cells. Despite this profound difference in cellular mechanisms, pain hypersensitivity in female mice is as robust as that in male mice. Taking into consideration sex differences in the spinal immune-neuronal signaling has important implications ranging from diagnostics, to therapeutics, to prevention of chronic pain.

Funding: Supported by CIHR, Krembil Fdn, and Northbridge Chair.

Robert Bonin, University of Toronto, Ontario

Plasticity of Pleasure and Pain

The relative pleasantness or unpleasantness of a sensory experience can be highly variable. The environmental, physiological, and cognitive context can profoundly affect how normally painful or pleasurable sensory stimuli are experienced. The perceived aversiveness or pleasantness of tactile stimuli can abruptly change in response to changes in physiological or environmental conditions. This 'affective' plasticity can be clearly observed in how our response to gentle stroking of the forearm by another person can feel pleasant or repulsive in different conditions. An abnormal response to socially-relevant physical stimuli may have profound effects on social behaviour, and possibly underlie disorders associated with abnormal social behaviour, such as Autism Spectrum Disorder. However, it is unclear how this rapid sensory plasticity arises or what physiological factors dictate whether identical tactile stimuli are perceived as pleasant or unpleasant. Using preclinical animal models, we have developed a combination of behavioural and optogenetic approaches to isolate and investigate this form of tactile sensory plasticity. We observed that mice exhibit a preference for gentle physical touch or optogenetic activation of MrgprB4+ sensory afferents that respond to gentle touch. However, the preference for optogenetic activation of MrgprB4+ afferents was abolished when stimulation was provided in a brightly-lit, aversive environment. We further revealed that the acute modulation of response to MrgprB4+ activation is mediated by the stress-related hormone, corticosterone. Overall, these findings shed light on the mechanisms underlying affective sensory plasticity driven by environmental and physiological factors and may indicate a new approach for reducing the unpleasantness of noxious and innocuous stimuli.

Jeffrey S. Dason, University of Windsor, Ontario

A cGMP-dependent protein kinase regulates a nociceptive-like escape behaviour through a plastic sensory circuit

Painful or threatening experiences trigger escape responses that are guided by nociceptive neuronal circuitry. Although some components of this circuitry are known and conserved across animals, how this circuitry is regulated at the genetic and developmental level is mostly unknown. To escape noxious stimuli, such as parasitoid wasp attacks, *Drosophila melanogaster* larvae curl and roll away from the stimulus. Rover and sitter allelic variants of the *Drosophila foraging* (*for*) gene differ in parasitoid wasp susceptibility, suggesting a link between *for* and nociception. By optogenetically activating cells associated with each of *for*'s promoters (pr1-4), we show that pr1 cells regulate larval escape behavior. In accordance with rover-sitter differences in parasitoid wasp susceptibility, we found that rovers have higher pr1 expression and increased sensitivity to nociception relative to sitters. *for* null mutants display impaired responses to thermal nociception, which are rescued by restoring *for* expression in pr1 cells. Conversely, knockdown of *for* in pr1 cells phenocopies the *for* null mutant. To gain insight into the circuitry underlying this response, we used an intersectional approach and activity-dependent GRASP to show that pr1 cells in the ventral nerve cord (VNC) are required for the nociceptive response, and that multidendritic sensory nociceptive neurons synapse onto pr1 neurons in the VNC. Finally, we show that activation of the pr1 circuit during development suppresses the escape response. Our data demonstrates a novel role of *for* in nociceptive behavior. Interestingly this function is specific to *for* pr1 neurons in the VNC, guiding a developmentally plastic escape response circuit.

Anne Simon, Western University, London, Ontario

Towards an understanding of the neurocircuitry underlying social spacing in Drosophila melanogaster

Historically vinegar flies (*Drosophila melanogaster*) were not considered a social species because they do not form elaborate social communities, as eusocial species like bees and ants do. However, flies display relatively complex social behaviours, such as aggression and courtship behaviour, and learning through communal living. As such, *D. melanogaster* has frequently been used in social behavioural studies, which led to deciphering for example circadian rhythm (Nobel Prize in Medicine and Physiology 2017). One particular behaviour of interest in my lab is the determination of social spacing. All motile organisms, from bacteria to humans, including *D. melanogaster*, display a preferred inter-individual (or social) distance that can be affected by genetics, experience and/or the environment. We and others have shown that social spacing in *D. melanogaster* can be influenced by a variety of intrinsic and extrinsic factors, such as mating status, social enrichment, genes, and environmental conditions. More recently, the neural bases of social spacing

are starting to be elucidated. Interestingly, several of the players – from neurotransmitters to post-synaptic proteins – are conserved through evolution. These results indicate that different types of animals can be used as tools to study social interactions and the potentially conserved underlying internal mechanisms or pathways that generate social behaviours.

Iva Zovkic, University of Toronto Mississauga, Toronto, Ontario

The role of distinct H2A variants in learning and memory

Memory formation is a complex and protracted process that is heavily reliant on learning-induced changes in gene expression, which are regulated by epigenetic factors. Our lab recently identified histone variants as novel epigenetic regulators of memory formation, whereby the histone variant H2A.Z acts as a memory suppressor. Many questions remain about the function of histone variants in the brain, including their temporally-specific functions, the basis for their dynamic regulation, and the distinct role played by different types of histone variants. I will discuss our latest efforts to address these crucial questions, as well as the emerging role of histone variants as therapeutic targets for memory decline.

Trainee Speaker Abstracts

O1

Effect of ATRX Neuronal Inactivation on Hippocampal Synaptic Plasticity in Mice

Radu Gugustea[1,3,4], Renee J. Tamming[4], Nathalie G. Bérubé[1,2,4], and L. Stan Leung[1,3]

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[3]Department of Physiology and Pharmacology, Western University, London, ON
[4]Division of Genetics and Development, Children's Health Research Institute, London, ON

ATR-X syndrome, an X-linked intellectual disability disorder, is caused by mutations in *ATRX*, which encodes an ATP-dependent chromatin-remodeling protein involved in histone deposition and regulation of gene expression. Mice with conditional ablation of *Atrx*in postnatal forebrain excitatory neurons (ATRX-KO) display impairments in long-term spatial memory. However, whether hippocampal synaptic transmission and plasticity are disrupted in ATRX-KO mice has not yet been investigated. To address this question, we used a 16-channel probe to measure long-term potentiation (LTP), a cellular correlate of memory, and input-output relation of paired-pulse responses following stimulation of several hippocampal synaptic pathways *in vivo* in urethane-anesthetized mice. Theta-burst stimulation (TBS) of stratum oriens and medial perforant path (MPP) were used to induce LTP in the CA1 basal and apical dendrites, respectively. Stratum oriens TBS induced robust basal dendritic LTP in CA1 of both ATRX-KO and control mice, while paired-pulse facilitation during baseline was lower in ATRX-KO mice, suggesting baseline impairments in synaptic transmission. TBS of the MPP induced CA1 distal apical dendritic LTP in control mice but was significantly decreased in ATRX-KO mice. LTP deficiencies in ATRX-KO mice were also identified in the trisynaptic circuit. Taken together, our findings demonstrate that loss of ATRX in glutamatergic neurons of the forebrain leads to defective hippocampal synaptic transmission and LTP. These abnormalities may underlie the memory impairments in the ATRX-KO mice.

Acknowledgements: Supported by NSERC grant (LSL) and CIHR grant (NGB).

O2

Delta-9-Tetrahydrocannabinol Engenders Cognitive Deficits and Dysregulates Prefrontal Cortical Single-Unit and Oscillatory Activity via Hippocampal Mitogen Activated Protein Kinase Stimulation

Roger Hudson[1,2], Tya Vine[2], Tony Jung[1,2], Walter Rushlow[2,3], and Steven R. Laviolette[2,3]

[1]Graduate Program in Neuroscience; [2]Department of Anatomy & Cell Biology; [3]Dept. of Psychiatry. University of Western Ontario, London, ON

Mnemonic and attentional deficits are common neurocognitive impairments associated with cannabis use, and constitute core features of schizophrenia and other psychiatric disorders. However, the contributions of precise neurocircuitry and neurobiological mechanisms to these pro-psychotic impairments remain unknown. Given that direct projections between the ventral tegmental area (VTA) and medial prefrontal cortex (mPFC) facilitate attention and working memory processing in the ventral hippocampus (VHipp), we explored the hypothesis that intra-VHipp delta-9-tetrahydrocannabinol (THC) dysregulates mPFC-VTA neural activity to elicit cognitive deficits via modulation of local molecular signaling cascades. THC elicited c-Jun N-terminal kinase (JNK)-dependent deficits in short-term and working memory, social cognition, and attentional output, without affecting sensorimotor gating. mPFC pyramidal phasic bursting activity, and the number of spikes per each burst were reduced by intra-VHipp THC. Power spectral density analyses demonstrated increased mPFC beta, gamma, and epsilon LFP band power following THC. Cross correlation analysis revealed diminished mPFC-VTA synchronization within theta and gamma bands following THC via an extracellular signal-regulated kinase (ERK)-dependent mechanism, suggesting aberrant functional connectivity between the two regions. Thus, THC reduces mPFC-VTA information flow via dissociable JNK-ERK signaling cascades to elicit cognitive deficits and attentional impairments, suggesting implications for cannabis phytochemicals in neuropsychiatric disorders.

Acknowledgements: Supported by a Vanier Canada Graduate Scholarship to RH; CIHR, NSERC, and MITACS.

O3

Neuronal Responses to Muscarinic Receptor Activation Change During Postnatal Maturation of the Medial Prefrontal Cortex

Ashutosh V. Patel[1], Myles B. St-Denis[1], Sierra A. Codeluppi[1],Kelsy S. J. Ervin[2] and Craig D.C. Bailey[1]

[1] Department of Biomedical Sciences, University of Guelph, Ontario
[2] Department of Psychology, University of Guelph, Ontario

Acetylcholine (ACh) activation of both nicotinic (nAChR) and muscarinic (mAChR) receptors within the rodent medial prefrontal cortex (mPFC) facilitates prefrontal-dependent cognitive functions. The objective of this study was to determine the contribution of specific mAChR subtypes toward ACh responses in pyramidal neurons located within layer VI of the mPFC. Whole-cell electrophysiological recordings were performed in mPFC layer VI pyramidal neurons sampled from male and female CD1-strain mice at postnatal day (P)15-20 and P60-100. Muscarinic responses to ACh application resulted in a prolonged excitation in all neurons and a transient initial inhibition only in a subset of neurons. The proportionof neurons exhibiting the transient inhibition, and the duration of this response, were significantly greater at P15-20 than at P60-100. Pharmacological experiments using mAChR subtype-selective antagonists revealed that both the M1 and M3 subtypes are necessary for the inhibition response in all experimental groups, whereas the M2 subtype contributes to the inhibition response in male mice only. These same experiments demonstrated that the M1 and M3 subtypes contribute to the excitation response in all experimental groups, whereas the M2 subtype contributes to the excitation response in adult mice only. Semi-quantitative RT-PCR performed using isolated mPFC tissue revealed that mRNA expression for mAChRs is greater at P60-100 than at P15-20. Ongoing analyses aim to determine whether the observed responses to mAChR activation correlate with the morphology of recorded neurons.
Acknowledgements: Supported by NSERC

O4

Intact synaptic signaling restrains Wnd/DLK-mediated axonal injury response

Laura J. Smithson[1], Lucas Junginger[1], Juliana Zang[1], and Catherine A Collins[1]

[1]University of Michigan

Neurons respond to injury by invoking plasticity mechanisms to remodel and/or repair damaged circuits, or by undergoing degeneration and death. For any of these responses, activation of the dileucine zipper kinase DLK, also known as *Wallenda* (Wnd) in *Drosophila*, is a key driver.[1]Wnd/DLK protein is actively transported in axons and becomes acutely activated following axonal injury. Despite the fact that many neurons use branched axons to make multiple synaptic connections, the majority of previously reported injury models remove all presynaptic connections made by neurons via complete axotomy of nerve fibers. Whether neurons respond similarly to single axon branch injuries as they do to complete axotomy is an underexplored question. To investigate the mechanisms that regulate Wnd/DLK activation and response to axonal damage, we developed a branched axon injury paradigm in *Drosophila* larvae. Our data indicate that trafficking and downstream signaling of Wnd/DLK is strongly influenced by injury location in axonal branches. Specifically, we found that Wnd/DLK signaling is only activated by injuries that completely remove all synaptic connections, and that the presence of a single synaptic branch is sufficient to restrain activation of this injury signaling pathway. This finding now draws our attention to synapses to understand the cellular and molecular mechanisms that regulate DLK-mediated injury signaling.

[1]Asghari Adib E., Smithson LJ., Collins CA. 2018. An axonal stress response pathway: degenerative and regenerative signaling by DLK. CurrOpinNeurobiol, 53:110-119.

Poster Abstracts

Neurophysiology

P1

Visually Responsive Neurons in the Primary Auditory Cortex in Awake Hearing Cats

Xiaohan Bao[1] and Stephen G. Lomber[1]

[1]Western University

Deaf subjects are identified to have enhanced visual abilities compared to hearing subjects. It is hypothesized that such behavioral compensation is provided by the functional cortical reorganization, in which the auditory cortex, deprived of normal acoustic input, is cross-modally reorganized to process visual information. While previous studies in primary auditory cortex (A1) have shown that deafness causes only small increases in cortical projections arising from visual cortex, it did significantly increase spine density in the supra granular layers of A1, suggesting synaptic plasticity in pre-existing visual inputs. In order to evaluate changes in auditory cortex following hearing loss, it is necessary to examine auditory and visual responses in auditory cortex prior to hearing loss. Therefore, in this project, hearing cats were trained to look at a fixation dot for 1 to 5 seconds, while extracellular activities from A1 neurons in response to auditory and/or visual stimuli were recorded through a 32-channel chronically-implanted electrode. Our preliminary data showed the presence of neurons that are visually-responsive or neurons whose auditory responses can be modulated by visual stimuli. These visual inputs are likely to be strengthened following deafness. In future studies, we will examine visual responses and visual modulation on auditory inputs in A1 of awake deaf cat.

P2

GSK3 Activity is Decreased in the Hippocampus of Male Mice Supplemented with Low-dose Lithium in Drinking Water

Rachel K. Fenech[1,2], Colton Watson[1], Adam J. MacNeil[1], Brian D. Roy[3], Val A. Fajardo[3] and Rebecca E.K. MacPherson[1,2]

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Alzheimer's disease (AD) is a neurodegenerative disease characterized byneurofibrillary tangles composed of hyperphosphorylated tau proteins and amyloid-beta (Aβ) plaques. Glycogen synthase kinase-3 β (GSK3β), a kinasethat remains constituently active until phosphorylated at its Ser9 residue, has been implicated in the development of AD pathologies.GSK3β is capable of inducing tau hyperphosphorylation and can phosphorylate amyloid-precursor protein (APP), influencing Aβ peptide production. Lithium (Li), a GSK3β inhibitor, has been suggested as an ADprophylaxis, howeverhigh doses areassociated with adverse effects. The purpose of this study was to examine the effects of low-dose Li on brain GSK3β activity. C57BL/6J male mice were given 10mg/kg/day Li or no Li in drinking water for 2 months(n=10-11/group) and the hippocampi were collected for GSK3 activity assay and western blot analyses. Li mice hadincreased serum Li concentrations ($p<0.0001$) and decreasedhippocampal GSK3 activity ($p=0.06$) as compared to control mice.However, no differences in pGSK3β Ser9, pAPP or pTauwas observed between control and Li mice. Changes in GSK3 activity without Ser9 phosphorylation changes may suggest that a longer supplementation is needed to affect significant changes in the brain. This initial work provides evidence that Li can inhibit hippocampal GSK3 activity. Future work will examine Li's potential beneficial effects in a diseased model (i.e. aged and metabolically-distressed mice). Thisis important toelucidate the efficacy of low-dose Li in the prevention of AD pathologies.

P3

Upregulation in neuronally-expressed CB_2 receptors in the spinal cord following nerve injury or chronic opioid administration

Patrick Grenier[1], Adam Sunavsky[1], and Mary C Olmstead[1]

[1]Department of Psychology, Queen's University, Kingston, ON

CB_2 receptors play a key role in modulating inflammatory and nociceptive pathways, and there is extensive cross-modulation between opioid and cannabinoid systems. Thus, we sought to map changes in CB_2 expression in glia and neurons within the lumbar spinal cord following surgery and chronic morphine treatment. 24 male rats were randomly

assigned to a chronic constriction injury (CCI) group to induce neuropathic pain, a sham surgery group, or a pain naïve group. Half the rats in each received ten days of saline; the other half received morphine (5mg/kg). On day 11 spinal cords were extracted and fluorescent immunohistochemistry was performed to double-label CB_2 and microglia (CD11b) or neurons (NeuN). DAPI was used to stain cell nuclei. Mean pixel intensity was determined in the deep and superficial dorsal horn for each antibody. Manual cell counts were performed as a secondary measure of CB_2 immunoreactive cells and to determine the degree of co-localization. Surgery rats had higher DAPI labeling compared to the naïves. CCI rats showed an upregulation of CD11b on the ipsilateral side indicative of spinal gliosis, but less NeuN labeling compared to shams and naives. A 3-way ANOVA showed small effects of surgery, larger effects of opioid treatment and very large differences between the deep and superficial dorsal horn. Most CB_2-immunoreactive cells co-expressed NeuN, though there was very little co-expression with CD11b.Neuronal expression of CB2 receptors in the spinal dorsal horn appears to be upregulated by nerve injury and by an even greater extent by chronic opioids.

Acknowledgements: Supported by CIHR and NSERC

P4

Electroporation of Cells in the Peripheral Olfactory Organ in *Petromyzon Marinus*

Abdulrahman Hamdoon[1], and Dr. Barbara Zielinski[1]

[1]Department of Biological Sciences, University of Windsor, Windsor, ON

In sea lampreys (*Petromyzon Marinus*), the olfactory system is of importance because it is used to detect cues in the form of odorants to perform activities such as feeding and reproduction. Olfactory sensory neurons detect cues and transmit sensory information to higher brain structures. The peripheral olfactory organ contains a large olfactory epithelium, and small diverticula called the accessory olfactory organ (AOO) that are linked by narrow ducts to the main olfactory epithelium. The AOO contains sensory neurons that project to the medial region of the olfactory bulb, where post-synaptic neurons project to the posterior tuberculum. AOO sensory neurons have been labelled previously by retrograde dye loading from the medial region of the olfactory bulb. This project aims to label the AOO cells by using an anterograde strategy, where fluorescent dextran was loaded into the nasal cavity. Various dye loading techniques included electroporation to increase the permeability of the cell membrane. These experiments encompassed several variables including the loading time, current intensity, continuous vs alternating current, and the use of detergents. In all cases, the cells of the main olfactory epithelium labelled robustly, whereas there was a low success rate of loading AOO cells, as the dye was stopped at ducts connecting the AOO to the main olfactory epithelium. These findings suggest that ducts may regulate odorant access to the sensory neurons in the AOO.

P5

Inhibition of DNA Methyltransferase Induces Melatonin Receptor Expression

Emily Hartung[1,2],Sumeya Mukhtar[1,2],Mahnoor Shah[3], Lennard P. Niles[2]

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[3]Molecular Biology and Genetics, McMaster University

The multiple physiological effects of the indole amine hormone melatonin, are mediated primarily by its two G protein-coupled MT_1 and MT_2 receptors. Our group has shown an upregulation of melatonin receptors following treatment withhistone deacetylase (HDAC) inhibitors, including valproic acid (VPA) and trichostatin A, in cultured cells and/or in the rat brain. VPA increases histone H3 acetylation at the MT_1 gene promoter region in rat C6 glioma cells, indicating that this epigenetic mechanism underlies its upregulation of MT_1 expression. Since HDAC inhibitors can also alter DNA methylation, the possible involvement of this second major epigenetic mechanism in the regulation of MT_1expression, was examined.C6 cells were treated with the DNA demethylating agent, azacytidine (AZA,1 - 25 μM), for 24h or 48h. Total RNA was extracted, and cDNA synthesized for PCR experiments. Western blotting was used to confirm inhibition of DNA methyltransferase 1 (DNMT1) expression by AZA. Treatment of C6 cells with AZA caused a significant upregulation of MT_1 expression, as compared with controls (DMSO 0.05%).Moreover, treatment with AZA (10 or 20μM) for 24h or 48h, suppressed or abolished DNMT1 protein expression. These results show that DNA demethylation plays a role in the regulation of the MT_1 receptor, consistent with the well-known effects of this epigenetic mechanism on gene transcription. Understanding the regulation of melatonin receptors, could provide avenues for enhancing the antioxidant, neuroprotective, oncostatic and other benefits of this hormone and its agonists.

Acknowledgements: Supported by NSERC.

P6

In Vivo Modulation of Microglial Activity using Chemogenetics

Aja Hogan-Cann[1,4], Diana Sakae[4], William Binning,[1,4] Matthew Maksoud[1,4], Valeriy Ostapchenko[4], Mohammed Al-Onaizi[4], Sara Matovic[4], Wataru Inoue[1,2,4], Wei-Yang Lu[1,2,4], Vania F. Prado[1,2,3,4], and Marco A. M. Prado[1,2,3,4]

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[4]Molecular Medicine, Robarts Research Institute, University of Western Ontario, London, ON

Microglia, the immune cells of the central nervous system, survey their surroundings and respond to external stimuli to maintain homeostasis in the brain.To do this, microglia express an array of receptors that allow them to receive and respond to signals from neighboring cells. Many of these receptors are G protein-coupled receptors, which regulate a variety of microglial functions through different signalling pathways. We have generated mice expressing either Gq (hM3Dq) or Gi (hM4Di) Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) selectively in microglia. These mutated muscarinic receptors no longer respond to their endogenous ligand acetylcholine, but they can be activated by clozapine-N-oxide (CNO) or clozapine, at doses that are inert at other receptors. In both Gq and Gi DREADD mice, the recombinant receptor is expressed selectively in microglia. Activation of microglial Gq or Gi DREADD by CNO initiates Gq and Gi intracellular signalling pathways, respectively. Furthermore, activation of either signalling pathway, by intraperitoneal injection of CNO, does not seem to affect baseline behaviour. Remarkably, chronic activation of microglial Gq signalling in mice, by CNO injection, decreased the expression of pro-inflammatory cytokines in the brains of LPS-injected mice. This chemogenetic method of manipulating microglial activity could therefore be applied to diseases where microglia dysregulation leads to neuroinflammation.

Acknowledgements: Supported by CGSM, CIHR, Alzheimer's Society of Canada.

P7

Time Course of Surgical Stress and the Role of Testosterone in the Modulation of Dendritic Morphology

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Gonadal and stress steroid hormones can dramatically alter hippocampal (HC) and medial prefrontal dendritic morphology which may underlie post-stress cognitive impairments. Our laboratory has previously shown that orchidectomy (ORCH) causes expansion of CA3 apical dendrites 10-days and 2-month after surgery compared to sham-operated (SHAM) rats. At 10-days, SHAM rats have truncated CA3 apical dendrites while testosterone (T) replacement partially restoresCA3 apical branching. However, the time course of surgical stress and the roles of glucocorticoids (GC) and T are unclear. We determined the time-course of acute stress and GC at 1-, 3- and 10-days. Unstressed rats treated with dexamethasone show atrophy of CA3 apical dendrites 3-days after treatment. To determine the role of T in the recovery of dendritic morphology, rats were either ORCH, ORCH+T replaced, SHAM or left intact, and sacrificed 1- and 2-months after surgery. At 1-month, ORCH rats had similar CA3 apical branching seen at 10-days. While ORCH+T and intact rats had comparable CA3 apical branching, the SHAM rats had decreased CA3 apical branching. By 2-months, CA3 apical dendrites of SHAM rats appeared to be almost completely recovered. However, surgery reduced the dendritic length of the longer CA3 apical dendrites, an effect that persisted even 1- and 2-months after surgery. No effect was seen in CA1 branching or HC dendritic spine density in any treatment group. Our results suggest that stress rapidly alters CA3 dendrites, that is in part mediated by GC, while T may modulate the recovery from surgical stress.
Acknowledgements: Supported by NSERC and the Ontario Veterinary College.

P8

Investigating the Neuronal Electrophysiological Properties in the Auditory Cortex of an Animal Model for Autism

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The contactin-associated protein-like 2 (*Cntnap2*) gene is highly associated with the occurrence of autism spectrum disorder (ASD), and disruptions in *Cntnap2* result in moderate to severe language impairments in humans. Importantly, the *Cntnap2* gene is not exclusive to humans and is expressed throughout the cortico-striato-thalamic circuit in other animals, and when knocked out in rodents it results in auditory processing deficits. The *Cntnap2* gene is hypothesized to be necessary for the normal neuronal development of the auditory brain. Neurons in auditory cortex of *Cntnap2*$^{-/-}$ rats are

predicted to have altered intrinsic membrane properties and excitability. To determine the role of *Cntnap2* in auditory processing, we used *in vitro* electrophysiology (whole-cell patch clamp technique) in juvenile *Cntnap2*$^{+/+}$, *Cntnap2*$^{+/-}$, and *Cntnap2*$^{-/-}$ rats to investigate the changes in membrane properties of neurons within the auditory cortex. Intrinsic membrane properties of cortical pyramidal cells and PV+ fast-spiking interneurons from cortical layers 2/3 were assessed. Specifically, NMDA and AMPA mediated glutamatergic, as well as GABA mediated inhibitory activities were assessed using various pharmacological agents. This study is currently in the data collection phase, with preliminary results expected by the time of the conference. These experiments will provide a novel look into how *Cntnap2* impacts the auditory brain at a cellular level, and shed light on the neural mechanisms underlying the altered auditory processing seen in *Cntnap2*$^{-/-}$ rats.

P9

Acute Interleukin-6 Treatment of SH-SY5Y Cells Increases AS160Phosphorylation Through AMPK

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IL-6 is a cytokine released from the brain with exercise. GLUT4 is expressed in the brain and can be recruited to axonal plasma membranes with neuronal activity through AMPK activation. The aim of this study is to examine: 1) if IL-6 results in AMPK activation in neuronal cells; and 2) if IL-6 increases the phosphorylation of proteins involved in GLUT4 translocation.Retinoic acid differentiated SH-SY5Y neuronal cells were treated with insulin (100nM) and two doses of IL-6 (10ng/mL and 20ng/mL) separately for 30min before being collected for Western blot analysis of Akt, STAT3, AMPK, and AS160. To examine the time course response cells were treated with 20ng/mL of IL-6 for 10, 20, 30 and 60 minutes followed by Western blot analysis of AMPK.Insulin treatment increased phosphorylation of Akt and AS160 ($p<0.05$). Treatment with the 20ng/mL dose of IL-6 resulted in phosphorylation of the α-subunit of STAT3 ($p<0.05$) as well as AS160 ($p<0.05$). Time course study results demonstrated that 20ng/mL of IL-6 resulted in phosphorylation of AMPK at 20 minutes ($p<0.05$).Our findings demonstrate that IL-6 can result in AS160 phosphorylation and that this occurs via a different signaling pathway than insulin (Akt vs AMPK). This is important because of the role AS160 plays in stimulating GLUT4 neuronal translocation.Together, this information will significantly increase our fundamental understanding of the processes that underlie how brain glucose metabolism is regulated.

Acknowledgments: Supported by NSERC

P10

Glucocorticoids Regulate G-Protein Coupled Estrogen Receptor Levels and Functional Signalling in Immortalized Hippocampal Neurons

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Estrogens exert neuroprotective and neurotrophic effects that are involved in modulating learning and memory. The recently identified G-protein coupled estrogen receptor (GPER) binds estradiol with high affinity, while mediating rapid neurotrophic and neuroprotective effects within the hippocampus. GPER's localization within cell bodies, dendritic spines, axons, and nerve terminals suggests that this receptor may play an important role in neuronal structure and function. Previous studies have shown that an acute behavioural stressor significantly impairs estradiol-mediated increases in spine density and this may contribute to thefemale's vulnerability to the detrimental effects of stress.However, the effects of stress hormone exposure on GPER expression and signaling remain poorly understood. To determine the effects of glucocorticoids on GPER, two novel lines of T-antigen immortalized murine hippocampal neurons were used. The mHippoE-14s and mHippoE-18s both exhibit high levels of the glucocorticoid receptor (GR) and GPER expression. Each cell line was treated with 10 nM of the synthetic glucocorticoid receptor agonist, dexamethasone, to investigate changes in GPER protein expression at 10 minutes, 1, 10, 24, and 48 hours following treatment. The female derived mHippoE-14 cell line exhibits reduced GPER expression and functional signaling after24-hour treatment with dexamethasone. This suggests that glucocorticoids may downregulate GPER mediated neurotrophic and neuroprotective effects of estradiol within the hippocampus.

Acknowledgements: Supported by NSERC and the Ontario Veterinary College.

P11

Sprint interval training elicits a higher brain derived neurotrophic factor response compared to continuous aerobic exercise

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Brain-derived neurotrophic factor (BDNF) is an exercise-induced neurotrophin mediating neuroprotection and synaptic plasticity. Circulating BDNF levels increase immediately post-exercise in proportion to intensity, however the effect of acute exercises (interval and continuous) at different intensities onthe BDNF recovery profile is unknown.Moreover, recently identified candidate modulators of exercise-induced BDNF expression in the periphery have yet to be investigated in parallel with BDNF. The purpose of the current study is to examine the response and recovery ofplasma BDNF and irisin following acute exercise of differing modalities and intensities. Eight healthy young adults completed four acute exercise sessions: 1) moderate-intensity continuous training (MICT); 2) vigorous-intensity continuous training (VICT); 3) sprint interval training (SIT); and 4) no exercise (CNTL). Blood samples were collected pre-exercise as well as immediately, 30 min, and 90 min post-exercise and plasma BDNF and irisin was analyzed via ELISA. The results show SIT as a more effective exercise modality in increasing plasma BDNF compared to MICT and VICT ($p < 0.05$), however elevated plasmatic BDNF recovered within 30-minutes post exercise ($p > 0.05$). No changes in plasma irisin were reported ($p > 0.05$). These results provide valuable insights in the design of running-based exercise-prescription optimizing for brain health through a neuroprotective BDNF response and the potential role of irisin in BDNF expression in acute exercise.

P12

Identification of the Frontal Eye Fields in the Common Marmoset using Microstimulation

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The frontal eye fields (FEF) play an important role in oculomotor control and visual attention. The common marmoset with its lissencephalic cortex is a promising model for exploring FEF microcircuitry. However, the precise location of the FEF in marmosets and its functional properties remain largely unknown.
Here we implanted 96-channel Utah arrays, in the left frontal cortex of two marmosets. Individual electrodes were stimulated while the monkey was head-restrained and freely viewing a video clip.
At sites in area 8aV, fixed vector saccades were evoked at short onset latencies. Evoked saccades were contraversive with direction mapping where downward saccades were elicited at more anterior sites and upward saccades at more posterior sites. Amplitude mapping was also observed at these sites with larger amplitude saccades evoked at anterior-medial sites and smaller amplitude saccades at more posterior-lateral sites.
Here we demonstrate a similarity of organization between FEF in marmosets and macaques. These results suggest the FEF in the common marmoset is located in area 8aV on the border of area 8aD and 6DR. Taken together, our data suggest that the common marmoset is both an appropriate and advantageous primate model for exploring FEF microcircuitry.

P13

Effects of a Preceding Sound on Neural Responses to a Succeeding Sound in the Rat's Auditory Midbrain

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The perception of a sound can be affected by another sound in an environment. This effect is dependent on the spatial and temporal relationship between the sounds. To understand neural mechanisms underlying this perceptual phenomenon, we recorded sound-driven electrical activities from single neurons as well as populations of neurons in the rat's midbrain auditory structure, the inferior colliculus. As neurons in this structure receive excitatory inputs driven by the

contralateral ear and inhibitory inputs driven by the ipsilateral ear, we used a sound with a fixed location at the contralateral ear to elicit responses. We found that both responses of individual and populations of neurons to such a testing sound were suppressed by a preceding priming sound. The strongest suppressive effect was observed when the succeeding testing sound immediately followed the preceding sound and the two sounds were colocalized at the contralateral ear. The effect was reduced when the preceding sound was spatially and temporally separated from the succeeding testing sound. The suppressive effect was most prominent in neurons that generated firing only at the onset of a sound. For neurons that generated sustained firing over the entire duration of stimulation, it was the initial component of the response that was most easily suppressed. Our results have provided an insight into neural processing of a sound in the existence of competing acoustic stimuli and helped us understand hearing in a natural acoustic environment.

Acknowledgements: Supported by NSERC, OGS, and University of Windsor

P14

Psychological Stress Modulates Synaptic Mechanisms for Immune-Induced HPA Axis Activation

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Immune-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis elevates the, glucocorticoid, ensuring effective resolution of inflammation. Dysregulation of this mechanism can lead to sepsis. The activation of the HPA axis relies on the activity of corticotropin releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVN). To activate the HPA axis, prostaglandin E_2 (PGE_2) can depress inhibitory GABAergic synaptic transmission on PVN-CRH neurons via presynaptic EP_3 receptor. The responsiveness of the HPA axis to inflammation can be modulated by prior psychological stress exposure. Here, I investigate potential synaptic mechanisms for the modulation of the HPA axis by prior psychological stress.I used whole-cell patch clamp electrophysiology in acute brain slices from naïve and acutely restrained mice to record GABAergic synaptic transmission on PVN-CRH neurons. I show acute restraint stress altersPGE_2-induced depression of GABA-mediated inhibitory synaptic transmission to PVN-CRH neurons.$G_{\alpha i/o}$-coupled EP_3 receptor-mediated GABA synaptic depression was intact after restraint stress. $G_{\alpha s}$-coupled EP_2 and EP_4 mediated presynaptic potentiation, which, contrary to my hypothesis, was not increased by restraint stress. Pharmacological blockade of EP_1mimickedstress. I predict that EP_1 may typically suppress EP_2 and EP_4-mediated presynaptic potentiation that can be unmasked by acute psychological stress. I explore a potential mechanism of prior psychological stress altering immune-induced HPA axis activation.

Acknowledgements: Supported by NSERC.

Neuroanatomy

P15

Differentiating the Ventral Tegmental Area and Substantia Nigra in Parkinson's Disease using Quantitative Susceptibility Mapping

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The midbrain dopaminergic system plays a major role in Parkinson's disease (PD).Degeneration of the substantia nigra pars compacta (SNc)causes motor symptoms; whereas, the later-affected ventral tegmental area (VTA) produces non-motor symptoms. Excessive iron accumulation in the midbrain is thought to cause this degeneration through mechanisms such as ferroptosis. Magnetic resonance imaging (MRI) can localize and quantify iron in the brain based on its magnetic susceptibility. Despite all this knowledge, there are no validated biomarkers of PD, but MRI has great potential for their discovery. Twenty early-stage PD patients and age-matched healthy controls were scanned once at 3T and 7T. Using quantitative susceptibility mapping (QSM) and R2* images, we segmented the midbrain structures and analyzed the average iron content in the SNc, VTA, and substantia nigra pars reticulata (SNr). Susceptibility values from QSM revealed significantly higher SNc iron content in early-stage PD patients compared to elderly controls at both field strengths. R2* mapping could only detect this difference at 7T suggesting this method is less sensitive than QSM. No significant group differences in iron content were found in the SNr or the VTA. To assess their value as biomarkers, we compared them using receiver operating characteristic curves, which suggest that QSM outperforms R2* at both field strengths. The increased iron load in the SNc of early-stage PD patients, best detected using QSM, could be the first diagnostic biomarker of PD following validation.

Acknowledgements: Supported by CIHR.

P16

Intratumoral Modulation Therapy Enhances Multi-Modality Treatment Platforms for Pediatric Diffuse Intrinsic Pontine Glioma

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Introduction: Intratumoral modulation therapy (IMT) is a putative new treatment modality that delivers non-ablative electrical stimulation directly into tumor-affected brain regions to induce tumor cell death. We have previously shown IMT reduces glioblastoma burden and now aim to assess the therapeutic potential of IMT in the high fatality brain cancer, diffuse intrinsic pontine glioma (DIPG). **Hypothesis:** We hypothesize that IMT combined with chemoradiotherapy will increase drug sensitivity and reduce DIPG viability. **Methods:** Patient-derived-DIPG cells were treated with 72-hour IMT (200kHz, ±2V), temozolomide (TMZ), radiation (RT) or combination therapies. The impact of single and multi-modal therapies was assessed using spectrophotometric and flow cytometry viability assays. Computer-generated electric field modeling was performed to predict and quantify IMT field strength, amplitude and geometry using low intensity, intermediate frequency sinusoidal waveforms. **Results:** MTT revealed significant loss of metabolic viability in DIPG cells treated with IMT compared to sham (>40%, n=3, $p<0.01$). TMZ and RT revealed a modest 19% and 28% reduction in viability respectively but increased significantly to 80% with concomitant IMT (>80%, n=3, $p<0.001$). **Conclusion:** This study provides first-time evidence of DIPG cell susceptibility to non-ablative electrical therapy and demonstrates the potential of IMT to enhance multi-modality treatment platforms currently available for DIPG.

P17

A Chemogenetic Approach to Understanding Prepulse Inhibition

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Our brains consistently receive an abundance of stimuli from the environment. An evolutionarily-conserved process that filters out sensory stimuli, sensorimotor gating, can be quantified via prepulse inhibition (PPI) of the acoustic startle response. Deficits of PPI are seen in a host of psychiatric illnesses, such as schizophrenia and autism spectrum disorder. The pedunculopontine tegmental nucleus (PPTg) and adjacent laterodorsal tegmental nucleus (LDTg) are major cholinergic centers of the mammalian brain and literature suggests that PPI is mediated by midbrain circuitry including inhibitory cholinergic projections from PPTg to the PnC. We recently debunked the PPTg cholinergic hypothesis using an optogenetics approach, leading to the current hypothesis. We predict that the PPTg and/or an adjacent structure mediates PPI albeit not via the cholinergic system.We used DREADDs (designer receptors exclusively activated by designer drugs) to transiently inhibit PPTg or LDTg cholinergic neurons inrats. An additional group receiveda general inhibitory DREADD (0.7ul or 1ul) bilaterally into the PPTg. Animals received i.p. or direct cannulae infusion of DREADD activator, clozapine-N-oxide (CNO) or saline.Transient inhibition of cholinergic PPTg or LDTg neurons did not affect PPI, however, the larger volume of general DREADD disrupted PPI upon i.p. administration of CNO.These findings continue the recent notion that the PPTg cholinergic neurons do not mediate PPI and propose the PPTg may act in synchrony with an adjacent structure in sensorimotor gating and its deficits.

P18

Source of GABAergic transmission at immature glycinergic synapses of brainstem

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During an early developmental period, some glycinergic synapses in the brainstem and spinal cord release predominately GABA, which activates $GABA_A$ receptors on the postsynaptic membrane. The function of this early GABAergic transmission is unknown but presumed to contribute to synapse maturation. Classically, the enzyme glutamic acid decarboxylase (GAD), which synthesizes GABA from glutamate, has been considered the sole source of GABA in neurons. Accordingly, GABAergic neurons typically express one or both of the two known isoforms of this enzyme,GAD65 andGAD67. To determine the source of GABA in immature glycinergic terminals of the auditory brainstem, we performed immunohistochemistry in brain tissue from rats aged postnatal day 0 to 28. We immunostained for GAD65 and GAD67, co-staining with markers for glial cells and synaptic terminals to verify cellular and subcellular location. In auditory brainstem, as in other areas, GAD65 was expressed in synaptic terminals whereas GAD67 was localized to neuronal cell bodies. However, during the peak period of GABA transmission in the first postnatal week, expression levels of both GAD65 and GAD67 were surprisingly low. We propose that immature glycinergic terminals of the auditory brainstem may acquire GABA through other means, as reported for example at co-transmitting synapses in the midbrain, rather than through the classical glutamic acid pathway.

Acknowledgements: Supported by NSERC and Developing Brains Fund

P19

Increasing Dendritic Spine Growth in the Prefrontal Cortex by Blockade of PIRB; A Potential Novel Treatment for the Cognitive Deficits of Schizophrenia

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Schizophrenia is a severe psychotic disorder and while patients currently have access to treatments for the positive and negative symptoms, no effective treatment exists to alleviate the cognitive deficits, which cause severe impairments to the quality of life of patients. Moreover, treatment efficacy is largely affected by the emergence of schizophrenia symptoms

past the point of major cortical plasticity. Recently, an immune receptor called paired immunoglobulin-like receptor B (PirB) has been identified to play an active role in inhibiting cortical plasticity throughout the lifespan. In addition, blocking PirB in adult rodents can enhance spine growth in different cortical areas, resulting in functional recovery in several disorders. Given that leading explanations for the basis of altered cognition in schizophrenia focus on a decrease in glutamatergic transmission in the prefrontal cortex (PFC),and in turn a reduction in the number of dendritic spines, blocking PirB holds great promise for both initiating cortical plasticity in adulthood and increasing cognitive function. In this study, we will behaviorally and molecularly assess the ability of PirB blocker to enhance PFC glutamatergic transmission and to ameliorate the cognitive deficits in our established animal model for schizophrenia that also shows decreased dendritic spines in layer 2/3 pyramidal neurons in the PFC. It is hypothesized that dendritic spine growth will increase to normal levels and cognitive function will recover in symptomatic rats treated with a PirB blocker compared to control animals.

Acknowledgements: Supported by BrainsCAN

P20

Structural Effects of Cross-Modal Plasticity Following Unilateral Early- and Late- Onset Deafness

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Following a period of sensory deprivation, cross-modal plasticity enables continued use of the deprived cortical regions, which causes a corresponding increase in function of the remaining sensory modalities. The vast majority of work on the neural effects of deafness has examined bilaterally deaf individuals, and consequently, treatments for the bilaterally deaf are relatively effective. In contrast, little is known regarding the changes in the structure of a unilaterally deaf individual's brain. Understanding the mechanisms by which cross-modal reorganization occurs provides the framework for treatments to effectively interface with the unique structure of deaf individuals' brain. The objective of this study is to determine the structural consequences of early- and late- onset unilateral deafness by examining the cytoarchitecture of the Mongolian gerbil brain. Using SMI-32 expression, auditory areas were visually delineated and the neuronal densities of the cortical layers within each area were quantified. Visual delineations made using SMI-32 stained sections were validated by comparing each area's unique laminar pattern of neuronal density. To date, we have examined the cytoarchitecture of gerbils with normal hearing to validate that SMI-32 staining is capable of discriminating between cortical regions. We will soon begin examining unilaterally deaf animals, where we hypothesize that any changes will occur contralateral to the deafened ear, and will depend upon the age of the animal at the onset of deafness. Ultimately, we hope that investigating the structural changes following unilateral deafness at various ages can narrow the scope of future study to improve treatments for the unilaterally deaf.

Acknowledgements: Supported by NSERC.

P21

Automated 3D Synapse Segmentation: An Iterative Thresholding Based Algorithm for Digital Image Analysis

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Anatomical analyses of neurons and neural circuits commonly require segmentation of synaptic signal from noisy fluorescence images, a task for which automated methods are especially useful. As global thresholding algorithms often result in overly large putative synapses, local thresholding algorithms have been developed to segment synapses in 3D. However, many such approaches are unwieldy, requiring intensive user interaction, substantial training on similar datasets, and/or significant computational costs for large datasets. Here, we describe a fully automated algorithm to segment synapses in 3D.
Our algorithm iteratively thresholds the 3D array at decreasing gray values, sums the binary images obtained at each threshold level, and then identifies local maxima in the summed binary image. Grayscale values of neighboring voxels are used to derive a local threshold value for each local maximum. These local thresholds are then applied to the neighborhoods of the local maxima in the original image, iteratively expanding the segmented clusters while observing constraints on synapse size.

We implemented this segmentation algorithm in MATLAB and tested it with confocal image stacks of brainstem tissue labeled for synaptic proteins. Our algorithm successfully segments synaptic clusters with nearby peaks and is robust to noisy (unfiltered) datasets, with significant reduction in computational time.

Support: NSERC, Developing Brains Fund

Neurochemistry

P22

A New Look at the Streptozotocin-treated Differentiated Human SH-SY5Y Neuroblastoma Cell Line as an In Vitro Model of Alzheimer's Disease: Erk/CREB/BDNF Involvement?

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Streptozotocin (STZ) is a toxic chemical that induces Alzheimer's disease (AD) and diabetes in experimental models. STZ triggers nitro-oxidative stress leading to insulin resistance (IR). IR is a core characteristic of diabetes and a risk factor for AD. Erk and Akt pathways are related to memory and are upregulated and down-regulated in IR and AD, respectively. CREB and its target BDNF promote memory and act upstream and downstream of Akt and Erk. In AD, Akt is down-regulated while activation of Erkis stage-dependent. In early AD, there is a transient activation of Erk, while at later stages, Erk phosphorylation is reduced. We used differentiated SH-SY5Y cells because of their human origin and cortical neuron-like properties. These cells were exposed to STZ to test the response oftheir Erk/CREB/BDNF and Akt pathways. The toxicity of STZ was determined by cytotoxicity assays. Changes in protein expression levels of phosphorylated Erk1/2, Akt, and CREB were evaluated by western blotting, with normalization to their total protein levels. Changes in BDNF mRNA expression levels were measured by real-time qRT-PCR. Our results showed that 1 mM STZ significantly reduced p-Akt, p-Erk1/2 and p-CREB without affecting their total protein levels. Moreover, BDNF mRNA expression levels remained unaltered. This study provides initial evidence that Erk/CREB signaling and Akt pathways are down-regulated by STZ in SH-SY5Y cells, resembling late-stage AD rather than IR. However, the lack of BDNF down-regulation does not resemble either AD or IR.

P23

Effects of Perinatal Δ^9 Tetrahydrocannabinol Exposure on Behavioural Inhibition in Adolescent Rats

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A growing body of evidence suggests that maternal cannabis use during pregnancy has harmful effects on neurocognitive development such as on executive functions. The primary psychoactive compound in cannabis, Δ^9-tetrahydrocannabinol (THC), has been shown to interact with the fetal endocannabinoid system which is critical for neuronal development. In this present study, we investigated the effects of perinatal THC exposure on behavioural inhibition, an executive function. Male and female rats (*n* = 48) were exposed perinatally to either 5 mg/kg THC (*n* = 24) or its vehicle (*n* = 24) from post-natal day (PND) 4-14. The Cued Response Inhibition Task (CRIT)was used as a measure of behavioural inhibition during the adolescent period of rodents. This operant task tests a rat's ability to inhibit a nose-poke response until the termination of a tone, then perform a nose-poke response within a brief window to receive a food reinforcer. Contrary to our predictions there was no effect of perinatal THC on the ability to inhibit a prepotent response or on the number of omissions. Taken together, these data suggest that perinatal exposure to THC had no effect on behavioural inhibition, at least within the dose and exposure protocol employed here.

P24

Tamoxifen Orestradiol Limited to the Induction Phase Enhance the Expression of Locomotor Sensitization to Nicotine in Ovariectomized and Intact Female Rats

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Estradiol (E2) is known to enhance nicotine-induced locomotor sensitization in rodent models, however whether estradiol is required during the induction phase and/or the expression phase is unknown. Here, ovariectomized rats were administered 5 µg estradiol benzoate (EB) or oil vehicle 30 min before injection of 0.4 mg/kg nicotine on two consecutive days (induction phase). Nine days later, half of the EB group was given EB and the other half oil and half of the oil group was given EB before injection of nicotine (expression phase). On each day locomotor activity (distance travelled) during 1 hour post-injection was measured, and the increase in activity from the induction period to the expression phase was the measure of sensitization. The effect of hormone treatment during induction was significant and the effect of hormone treatment during expression was not: Rats given EB during induction had enhanced sensitization relative to the OIL group

($p < 0.001$). These results were replicated in Expt 2., which involved 10 µg of E2 instead of EB. Next, gonadally intact (Expt 3) or OVX (Expt 4) rats were administered the selective estrogen receptor modulator tamoxifen (1 mg/kg) during the induction phase only. Tamoxifen enhanced expression of sensitization relative to OIL treatment in both intact and OVX females. Although EB, E2, and tamoxifen all enhanced sensitization, EB and E2 are agonists of estrogen receptors, whereas tamoxifen is an antagonist of intracellular estrogen receptors [ERα/ERß] and an agonist of membrane bound g-coupled protein estrogen receptor 1 [GPER1]). Thus the enhancing effects of estradiol during induction may involve membrane estrogen receptors rather than ERα and ERß.

Acknowledgements: Supported by NSERC.

P25

The anxiolytic drug, Buspirone, abolishes aversive stimulus induced hyperactivity in juvenile zebrafish (*Danio rerio*)

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Avoidance of aversive situations has high fitness value. However, the mechanism underlying such responses are not well understood. Psychopharmacology may help illuminate these mechanisms. Due to their evolutionary conservation, zebrafish are responsive to drugs utilized in the human clinic, an example of which is anxiolytics. Previously, zebrafish exposed to buspirone, an anxiolytic drug, were found to exhibit decreased anxiety-like responses. However, interpretation of these findings is controversial as some of the responses may have been unrelated to anxiety. Here, we utilize juvenile zebrafish, of an age not previously tested, in a novel fear-inducing paradigm, a tapping assay. In this task, the experimental zebrafish without any disturbance in an open tank for 5 min, and subsequently receive vibration, a tap, an aversive stimulus delivered once a min for the next 10 min. We employ3concentrations of Buspirone HCl, a medication prescribed for generalized anxiety. We immerse each experimental fish (n=71) to one of the drug solutions for 1 hour, a between subject experimental design. In response to tapping, control zebrafish exhibited elevated activity (increased swim speed). However, zebrafish of all three buspirone groups showed no such aversive stimulus induced hyperactivity. These results demonstrate that buspirone did not have an overall activity reducing effect but only blunted the aversive stimulus induced behavioural response. Thus, the “tapping-essay” is a simple and effective method to induce anxiety in juvenile zebrafish, and the effect of buspirone can be quantified with it. We hope that our pilot study will enhance our ability to use zebrafish to test potential anxiolytic properties of novel compounds, and that, in the future, it will also lead to better understanding of underlying mechanisms.

P26

Glucocorticoid Regulation of Dual Specificity Phosphatase 6 (DUSP6) in a Mouse Hippocampal Cell Line

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Dual Specificity Phosphatase 6 (DUSP6) is a specific negative regulator of ERK1/2, a kinase protein that is involved in neurogenesis and has been shown to have neuroprotective effects.DUSP6 is downregulated in depression in a sex-dependent manner (Labonte et al. Nat. Med. 2019 23;1102-1111) suggesting that it may be involved in the etiology of sex-dependent neurological disorders. Previous studies in our lab have shown that hydrogen peroxide (H2O2) treatment downregulates DUSP6 in a neuroblastoma cell line, likely as a result of cellular stress (Mendell and MacLusky, Neurosci Lett. 2019 Mar 23;696:60-66).Whether physiological stress has a similar impact on DUSP6 is not known. The goal of this study was to determine if glucocorticoid treatment also downregulates DUSP6. The immortalized embryonic mouse hippocampal cell line mHippoE-14 was treated with and without10 nMdexamethasone (DEX). RNA and protein were collected over the following1- 48-hour. Quantitative PCR and western blotting indicate that DEX downregulates DUSP6 expression. Preliminary results suggest that reduction in trophic factor support (via reduction in the serum content of the medium) may also reduce DUSP6 expression. Glucocorticoid and cellular stress-induced downregulation of DUSP6 may have implications for neurological diseases involving abnormal ERK phosphorylation.

Supported by NSERC and the Ontario Veterinary College.

P27

THC Hypernausea: Investigating Mechanisms of Aversive Effects of High Dose Cannabinoids

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Δ9-tetrahydrocannabinol (THC), a partial agonist of the cannabinoid 1 receptor(CB_1R), is known to treat nausea/vomiting in humans and animals. Paradoxically, findings in animals, and characterization of Cannabinoid Hyperemesis Syndromein humans suggest that high doses of THC can also *produce* nausea/vomiting. The mechanism underlying THC-induced nausea remains unclear. It is hypothesized that a dysregulation of the endocannabinoid (eCB) systemis involved. Conditioned gaping in the taste reactivity paradigm, a rat model of nausea, was used to examine the nauseating effects of THC. High doses of THC (5 and 10 mg/kg), but not a low dose (0.5 mg/kg) produced nausea in rats via its action on the CB_1R. PCR analysis revealed that 10 mg/kg of THC produced upregulation of the degrading enzyme of the eCB, 2-arachidonoyl glycerol, (2-AG), monoacylglycerol lipase (MAGL), in the hypothalamus, which may contribute to an overactive stress response. Indeed, pre-treatment with a MAGL inhibitor (MJN 110; 10 mg/kg) interfered with THC-induced nausea. The ability of the β-adrenoreceptor antagonist, propranolol, to interfere with THC-induced nausea was also evaluated. A dose of 5 mg/kg propranolol attenuated THC-induced nausea. These data support the hypothesis that THC-induced nausea may be a result of an overactive stress response due to eCB alterations. Ondansetron (0.1 and 0.01), a $5\text{-}HT_3$ antagonist and typical anti-emetic, which does not alleviate THC-induced nausea in humans, did not interfere with THC-induced conditioned gaping in rats, further supporting a stress mediated effect.

Acknowledgements: This research was supported by grants from NSERC and CIHR to L.A. Parker.

P28

Isoform-dependent toxicity in *Drosophila* models of Spinocerebellar Ataxia Type 3

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The most commonly inherited dominant ataxia, Spinocerebellar Ataxia Type 3 (SCA3) is caused by a CAG repeat expansion that encodes an abnormally long polyglutamine (polyQ) repeat in the disease protein ataxin-3, a deubiquitinase. Two major full-length isoforms of ataxin-3 exist, both of which contain the same N-terminal portion and polyQ repeat but differ in their C-termini; one (denoted here as isoform 1) contains a motif that binds ataxin-3's substrate, ubiquitin, whereas the other (denoted here as isoform 2) has a hydrophobic tail. Most SCA3 studies have focused on isoform 1, the predominant version in brain, yet both forms are expressed and a better understanding of their relative pathogenicity is needed. We took advantage of the fruit fly *Drosophila melanogaster* to model SCA3 and examine the toxicity of each ataxin-3 isoform. Our *Drosophila*-based assays reveal isoform 1 to be markedly more toxic than isoform 2 in all fly tissues. Reduced toxicity from isoform 2 coincides with much lower protein levels as a result of expedited degradation. When isoform 2 protein levels are engineered to be comparable to isoform 1, isoform 2 is no less toxic. Additional studies indicate that isoform 1 is more aggregation-prone than isoform 2. According to our results, although both full-length ataxin-3 isoforms are neurotoxic, isoform 1 is likely the primary contributor to SCA3 disease pathogenesis due to its expression at higher levels. Our findings provide new insight into the biology of this ataxia and the cellular processing of the underlying disease protein.

P29

The Effect of Varenicline Administration on Ethanol Consumption in a Lower Alcohol Drinking Rat Strain

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Alcohol and tobacco consumption frequently co-occur in the human population. Varenicline is currently the most effective non-nicotine replacement smoking cessation aid, but its impact on ethanol reinforcement is mixed in the literature. Therefore, we assessed the effects of varenicline pretreatment on ethanol self-administration at gradually increasing costs

in a lower-drinking rat strain.Male Sprague-Dawley rats underwent sucrose fading until they learned to lever press for 0.01 ml of 15% ethanol. We then assessed the effect of varying doses of varenicline pretreatment (0, 0.3, 1, and 3 mg/kg, s.c.) on ethanol consumption across increasing fixed-ratio schedules (FR1, FR2, FR5, FR10, FR15). Each FR schedule consists of 11 daily sessions of varenicline or saline pretreatment 15 min prior to a 50 min self-administration session. The first two days of each schedule are baseline saline days, followed by eight days of treatment with each rat exposed to all the doses in two unique orders, and one final saline day.Varenicline pretreatment dose-dependently increased ethanol consumption at low FR schedules rather than high schedules and enhanced ethanol demand by decreasing sensitivity to increasing cost. These results show that varenicline treatment may increase alcohol use in non-dependent drinkers.

P30

Beyond Amyloid: The Metabolic Regulator P66SHC as a Potential Therapeutic Target for Alzheimer's Disease

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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 CNS cells are resistant to Aßinsult.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 p66Shchas been shown to shift the cellular metabolic state to promote OXPHOS and repress 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. We overexpressed p66Shc and knocked down endogenous p66Shc in rodent neuronal and glial cell lines, to determine the effect of p66Shc activation on metabolic activity. Expression and activation of p66Shc repressed glycolytic enzyme expression and increased mitochondrial activity and ROS levels. The opposite effect was observed when p66Shc was knocked down. Activation of p66Shc increased sensitivity to Aß toxicity, whereas silencing p66Shc protected cells from Aß insult. Thus, expression and activation of p66Shc renders CNS cells more sensitive to Aß toxicity by promoting OXPHOS while repressing aerobic glycolysis, andp66Shc may represent a potential therapeutically relevant target for AD.

Acknowledgements: Funded by NSERC.

P31

Effects of Perinatal and Acute Δ^9-Tetrahydrocannabinol on Behavioural Inhibition in the Go/No-Go Task

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There is evidence that the endocannabinoid system plays a role in fetal neuronal development and that *in-vitro* exposure to cannabis can produce long-term consequences towards neurocognitive development. The present study examined both the long-term, neurocognitive developmental effects of perinatal Δ^9-Tetrahydrocannabinol (THC) exposure and the short-term effects of acute THC exposure on behavioural inhibition in the Go/No-Go task. Twenty-four female and 24 male CD(SG) IGS rats were injected subcutaneously from postnatal days (PND) 4-14 with THC at a dose 5mg/kg in a volume of 5 ml/kg or with a vehicle (VEH). Subjects were originally tested on a Cued Response Inhibition Task (CRIT) that used the same cues as the Go/No-Go task, so formal Go/No-Go training was bypassed. Experiment 1 studied the long-term effects of perinatal THC exposure across a 10-day period. Results revealed that learning on the task occurred, indicating that the CRIT and a lack of formal Go/No-Go training was sufficient to allow for learning. Experiment 2 studied the acute effects of THC across 4 doses (0, 1, 2, and 4 mg/kg) with a repeated measures design. There were higher hits and false alarms for the low dose compared to the high dose and the placebo, and for the moderate dose compared to high dose. There was not a difference between groups based on perinatal THC exposure in either experiment. Results may not be indicative to all facets of impulsivity and further research on the long-term effects of perinatal THC exposure is required.

P32

Gene Expression Analysis After Administration of PAOPA, an Allosteric Modulator of Dopamine D2 Receptor

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The allosteric modulator of the dopamine D_2 receptor,3(R)-[(2(S)-pyrrolidylcarbonyl)amino]-2-oxo-1-pyrrolidineacetamide (PAOPA),has demonstrated the potential to treat negative and cognitive symptoms associated with schizophrenia. It was hypothesized that PAOPA administration would significantly alter gene expression in the striatum of Sprague-Dawley rats compared to controls. RNA sequencing results were analyzed for differential expression using Cuffdiff. These results revealed a significant overexpression in several genes. The calcium-binding protein, parvalbumin (PVALB) was further investigated. RT-qPCR demonstrated that PAOPA significantly increased mRNA expression of PVALB *in vivo*. PVALB can modulate gamma-aminobutyric acid (GABA) neuron activity and potentially control impaired gamma band oscillations which are an underlying cause of cognitive schizophrenic symptoms. The implication of PVALB in schizophrenia provides further support that PAOPA has the potential to treat schizophrenic symptoms. Further research should analyze changes in PVALB protein levels using Western blotting and the effects of PAOPA on PVALB expression should be investigated in an animal model of schizophrenia.

P33

The Effects of TP5, a CDK5/P25 Inhibitor, in Human Neuroblastoma Cell Line and C. Elegans Models of Parkinson's Disease

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Parkinson's Disease (PD) is a neurodegenerative disease that is characterized by impaired motor functions due to the premature death of dopaminergic neurons in the nigro striatal pathway. Current non-invasive treatments are problematic as they only marginally increase striatal dopamine levels but fail to halt or reverse the course of neuronal death. Proactive approaches that could slow the progression of PD and maintain a healthy population of dopaminergic neurons are necessary. CDK5 binds to p25 to induce cell death and this complex is hyperactivated in PD which results in dopaminergic neuronal loss. The purpose of this study is to useTP5to block CDK5/p25 in an *in vitro* and *in vivo* model to confirm therapeutic effects in PD. The human neuroblastoma cell line and the nematode Caenorhabditis elegans were exposed to paraquat (PQ), an oxidative stressor, to exhibit PD's phenotypes. TP5 was administered prior to PQ exposure to determine its neuroprotective effects and after to examine its neurorestorative effects. Compared to the cells exposed to PQ alone, TP5 was also observed to protect neurons against PQ through increased cell viability ($p<0.05$). In the C. elegans system, TP5 demonstrated both neuroprotective and neurorestorative effects. Worms that were exposed to PQ alone had an 83% neurodegeneration, whereas the worms exposed to PQ and later injected with TP5 had a 57% neurodegeneration ($p<0.05$).Together, these results indicate that TP5 can act as a potential treatment towards PD based on the models that display PD's phenotype by targeting the CDK5/p25 pathway.

Acknowledgements: Supported by CIHR and NSERC, Canada

Behavioural Neuroscience

P34

The anxiolytic effect of buspirone hydrochloride on two different strains of juvenile zebrafish.

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Anxiety still represents a major unmet medical need as a large proportion of patients do not respond to the present anxiolytic drugs. The zebrafish may be particularly appropriate for this analysis because in addition to having several conserved features with mammals, drug administration can be employed in a non-invasive manner, i.e. via immersing the fish into the drug solution. Here we investigate the effects of buspirone hydrochloride, an anxiolytic drug often employed in clinics. We utilize two genetically distinct strains of zebrafish, AB, a genetically highly homogeneous quasi-inbred strain, and WT, a genetically highly heterogeneous wild type population. Juvenile (10-13day post-fertilization old) zebrafish were placed singly in petri dishes (3.5 cm diameter) containing one of four buspirone concentrations (0 mg/l, 5mg/l, 20mg/l and 80mg/l) for an hour, with each fish receiving only one exposure and one concentration treatment. Subsequently, the behaviour of the experimental zebrafish was recorded for 30 min using Ethovision video tracking software. Numerous behavioral parameters were extracted including turn angle, total distance moved, angular velocity, cumulative duration of immobility, and cumulative duration of thigmotaxis. Data were analyzed using SPSS. We found buspirone to increase swim speed, turn angle and interestingly, the duration of immobility, in both strains. At this point we do not know whether these behavioural changes represent anxiety reducing effects. Thus our study may contribute to behavioural fingerprinting of anxiolytic drugs.

P35

Setting the Occasion with Morphine: Exploring the Impact of Differential Learned Experiences on the Incentive Value of an Interoceptive Morphine Stimulus

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Occasion setting is a type of hierarchical associative learning wherein a contextual stimulus, the occasion setter (OS), can disambiguate the relationship between a conditioned stimulus and unconditioned stimulus and become a discriminative guide of behaviour. The behavioural and neurological mechanisms underlying how learned associations influence the incentive salience of stimuli and shift in motivational value are largely unknown. This research investigates the impact of appetitive and non-appetitive learned associations with morphine on subsequent motivation for that morphine stimulus. Male and female Sprague-Dawley rats are assigned to feature positive (FP) or feature negative (FN) training. All rats are given daily intermixed morphine or saline sessions containing eight white noise (WN) presentations. For FP rats, on morphine sessions, each WN offset is followed by sucrose delivery; on saline sessions, sucrose is withheld. For FN rats, sucrose is delivered on saline sessions and withheld on morphine sessions. Investigations of how such conditioning alters the value of the interoceptive drug stimulus are limited. One study showed FN training with nicotine imbues nicotine with conditioned inhibitory properties. Further, a recent study demonstrated enhanced incentive value for an external FPOS, but no studies have assessed this with drug stimuli. Thus, we hypothesize that an appetitive learning history would imbue a higher value for morphine compared to a non-appetitive learning history.

P36

The Effect of Oleoyl Glycine on Reinstatement of Previously Extinguished Morphine Place Preference in Rats

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Oleoyl glycine (OlGly) is a newly isolated fatty acid amide and an endogenous cannabinoid of the body's endocannabinoid system. Recently, OlGly has been shown to interfere with nicotine reward and dependence in mice. Using place conditioning procedures, we have shown OlGly interferes with the aversive properties of opioid withdrawal in rats, but did

not influence the rewarding properties of opioids. This experiment sought to extend on these findings by determining the effect of OlGly on the reinstatement of a morphine conditioned place preference in Sprague Dawley rats.
Rats (n=36) received four conditioning cycles with injections of saline or 10mg/kg morphine (24h apart; counterbalanced) 10minbefore placement conditioning chambers with tactically distinct grid or hole flooring (counterbalanced) for 30min. Following conditioning, rats received 4 10min test trials until the morphine place preference had extinguished. Twenty-four hr following the final extinction trial, rats received a 10 min reinstatement test during which they were injected with VEH, 1.0 mg/kg, or 5.0 mg/kgOlGly10min prior to a priming injection of 2.5 mg/kg morphine 10min before placement in the test chambers.
At 1 and 5 mg/kg, OlGly did not interfere with the reinstatement of a previously extinguished morphine conditioned place preference. Taken together, these findings suggest OlGly only interferes with the aversive properties of opioid withdrawal, without interfering with the drug's rewarding properties. Therefore, OlGly may be a new therapeutic target for reducing the impact of opiate withdrawal.

Supported by research grants to LAP from NSERC, CIHR and PlantExt.

P37

The memories that linger: The effect of acute opiate withdrawal and conditioned opiate withdrawal on memory consolidation

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Opiate withdrawal can be associated to a context through classical conditioning to produce conditioned withdrawal. To explore the role of conditioned withdrawal in memory processes, this research investigated whether conditioned withdrawal could impact memory consolidation. Two experiments in males Sprague-Dawley rats compared the effects of naltrexone-precipitated withdrawal and conditioned morphine withdrawal on consolidation of object recognition memory. In Experiment 1, 1 and 3 mg/kg naltrexone was administered immediately, or 6 hours, post-sample to morphine-naïve and morphine-dependent animals (osmotic mini-pumps; 10 mg/kg/day). The post-training effects of naltrexone were re-tested 7 days following removal of the pumps. In Experiment 2, morphine-naïve and morphine dependent rats were confined for 2 hours in a distinctive chamber (CS+) following naltrexone injections (1 or 3 mg/kg) and in another chamber (CS-) following vehicle injections. This was repeated for 10 days: 5 naltrexone/CS+ pairings and 5 vehicle/CS- parings. The effects of immediate or delayed (6 hrs) post-sample exposure to the CS+ and CS- were tested during dependence, and 7 days following removal of pumps. Experiment 1 found that 3 mg/kg naltrexone enhanced object recognition memory when administered immediately, but not 6 hours, post-training in morphine dependent and post-dependent, but not morphine-naïve, rats. During conditioning in the CS+, Experiment 2 found that naltrexone supressed locomotor activity, caused rapid body weight loss, and increased frequency of wet dog shakes in morphine-dependent rats only. When confined in the CS+ without naltrexone injections, rats displayed suppressed locomotion, weight loss and wet-dog shakes. More importantly, exposure to CS+ immediately, but not 6 hours, post-training enhanced object recognition memory during dependence and post-dependence. These experiments indicate that both acute precipitated and conditioned withdrawal have significant and persistent faciliatory effects on memory consolidation. This suggests that conditioned effects on memory processes can play a significant role in addictive behaviours.

Acknowledgements: Supported by NSERC.

P38

The Interplay between D2-type Dopamine Receptors in the Dorsal Hippocampus and Gonadal Sex Hormones in the Modulation of Social Learning in Male and Female Mice

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Dopamine (DA) is a catecholamine that modulates many types of cognition including feeding, reward and social behavior. In mice, DA receptors in the dorsal hippocampus (HPC) have been directly implicated in social learning. In the social transmission of food preference (STFP) paradigm the preference for a novel flavored food is transferred between conspecifics following social interaction. Antagonizing D2-type DA receptors in the dorsal HPC blocked the STFP in female but not male mice suggesting that D2-type DA receptors interplay with sex hormones to regulate social learning(Matta et al., 2017). Estrogens have been directly implicated in the STFP, but the role of androgens has never been investigated. However, androgen treatment increasedHPC DA release.Here, weinfused D2-type DA receptor antagonist raclopride (18 µg/µL, 20 µg/µL, or saline) into the dorsal HPC (0.5 µL per hemisphere) of gonadally intact and

gonadectomized male and female “observer” CD1 mice prior to a 30-minute social interaction with a recently fed same-sex familiar “demonstrator”. Findings reveal that raclopride shortened the duration of a food preference in gonadally intact males and females, but not ovariectomized females.Castration alone dramatically reduced the duration of a food preference. Findings suggest that 1. gonadal female sex hormones interact with D2-type DA receptors in social learning 2.gonadal male sex hormones modulate social learning in males. Thus, there appears to be a sex difference in the way gonadal hormones and D2-type DA receptors mediate social learning in the dorsal HPC.
Acknowledgements: Supported by NSERC.

P39

Sexually dimorphic effects of propionic acid in adult rats: implications for an animal model of autism spectrum disorder

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Autism spectrum disorder (ASD) is a developmental disorder of variable severity characterized by impairments in social interaction and communication as well as restricted and repetitive patterns of movement. Past research suggests that certain gut and dietary factors may transiently worsen symptoms in ASD. Propionic acid (PPA) is a short chain fatty acid and an important intermediate of cellular metabolism. PPA is also a by-product of a subpopulation of human gut enterobacteria. Previous studies have shown that treatment with PPA can create both brain and behavioural responses in rats that are characteristic of ASD in humans. A strong and consistent male bias in ASD prevalence has been observed, and several sex-differential genetic and hormonal factors have been suggested to contribute to this bias. Past studies have reported a neuroprotective effect of the sex hormones prolactin and estrogen, for both hippocampal neurodegeneration and neuroinflammation, which have been proposed as potential etiological mechanisms in autism. Very little research has examined the effects of PPA in females. The present study explored putative sex differences in the effects of PPA on a rodent behavioral ASD phenotype. Male (N = 16) and female (N = 16) rats were systemically treated with PPA (500mg/kg) or PBS control and tested in a light-dark anxiety procedure. PPA-treated females displayed similar patterns of anxiety-like behaviour (i.e. duration of time spent in the light chamber and nosepokes into the light chamber) to PPA-treated males, which differed significantly from PBS treated rats.

P40

The Behavioural Effects of Early Adolescent Lipopolysaccharide Exposure in Adolescent and Adult Male and Female Rats

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There is accumulating evidence for sex differences in the behavioural, physiological, and immunological effects of infection. Lipopolysaccharide (LPS), a cell wall component of Gram-negative bacteria, has been effectively used to examine these differences. Generally, males are more susceptible to infection than females. Age-related changes are a contributing factor to this sex difference. There have been limited investigations of: (1) the impact of adolescent infection, (2) the long-term effects in later adolescence compared to adulthood, and (3) whether or not there are sex differences in these long-term effects. The present study was designed to examine sex differences in the long-term effects of LPS measured in late adolescence and adulthood following early adolescent LPS exposure. Thus far, eight male rats were assigned to each of the LPS (0.2 mg/kg dissolved in 0.9% NaCl) and vehicle control (0.9% NaCl) groups and received early adolescent intraperitoneal injections on postnatal days 30 and 32. After a five-day washout period, (1)general locomotor activity; (2) anxiety; (3) social behaviour; (4) memory; (5) acoustic startle response (ASR); and (6) sensorimotor gating were examined.A physiological tolerance to LPS was established.LPS increased locomotor activity in adolescence, decreased anxiety and social initiations in adolescence and adulthood, and had no significant effects on ASR and sensorimotor gating. Upon completion of this project, variations in age and sex will be accounted for to better our understanding of differences in the behavioural effects of LPS.

Acknowledgements: Supported by NSERC.

P41

Automated touchscreen tasks reveal early cognitive dysfunction caused by mutant TDP-43 in an FTD/ALS mouse model

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TAR-DNA-binding protein 43 (TDP-43) misfolding and aggregation is a major pathological hallmark of Fronto-Temporal Dementia (FTD) and Amyotrophic Lateral Sclerosis (ALS). FTD/ALS are characterized by motor and cognitive impairments. However, robust cognitive phenotypes related to TDP-43 proteinopathy have not been established for most mouse models of FTD/ALS. In this study, we used automated touchscreen technology to assess executive function in the transgenic FTD/ALS mouse model TDP-43^{Q331Klow}. Reported previously, these mice show motor impairments at 12 months of age, however, cognitive dysfunction has not been evaluated. Attention, learning and cognitive flexibility (constructs affected in FTD/ALS) were assessed inTDP-43^{Q331Klow}male mice using the Five Choice Serial Reaction Time Task (5-CRSTT), Pairwise Visual Discrimination (PVD) task and Reversal Learning. In 5-CRSTT, TDP-43^{Q331Klow}mice (5-6month-old) present higher omissions (missed targets) and also perseverative, compulsive-like behaviour. In the PVD task TDP-43^{Q331Klow} mice were impaired in both the acquisition and reversal phases of the task. This suggests an impairment in learning and perhaps, taken together with the perseverative phenotype in the 5-CRSTT, cognitive/behavioural flexibility. These results indicate that the TDP43^{Q331Klow} mice present cognitive/behavioural impairment similar to those observed in humans affected by these diseases, suggesting that this mouse model may be useful for studying the neuropathological basis of cognitive impairment in FTD/ALS, and developing new therapeutic approaches.

Support – ALS Society Canada, BrainsCAN

P42

Response in the Avian Hippocampal Formation to Incremental Changes in Context

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

P43

Prefrontal Morphology and Cognition in the Goto-Kakizaki Rat Model of Diabetes

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The Goto-Kakizaki (GK) rat provides an animal model of type 2 diabetes that can illustrate the mechanisms by which the disease adversely affects cognitive function. In the present study, GK rats and age-matched Wistar rats were tested in a perceptual attentional set-shifting task to assess putative prefrontal-dependent executive functioning. Day1 of the task involved training rats to dig for food rewards and discriminate between different odours, digging mediums, and textures. Day 2 of the task consisted of a series of 7 shifts including discriminations, an intradimensional shift, an extradimensional shift, and 3 reversals. GK rats required significantly more trials to reach criterion in the discriminations, but not the other

shifts. Duration of the discrimination and reversal 1 trials were also significantly greater for the GK rats. Urinary glucose tests validated hyperglycemia both before and after the task. Golgi-Cox staining was used to examine pyramidal neuron spine densities in the prelimbic cortex. Spine densities were significantly decreased for GK rats in both Layers II/III and V in the basal and apical dendrites. Results suggest that GK rats have morphological changes in the prefrontal cortex despite having preserved executive function. The cognitive deficits observed in GK rats appear to be related to altered perception rather than executive functioning.

Acknowledgements: Supported by NSERC.

P44

Spontaneous Mimicry of Emotional Facial Expressions as a Function of Trait Sadism

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Using electromyography (EMG), it has been shown that facial muscles imperceptibly mirror the facial expressions of others, a phenomenon referred to as spontaneous facial mimicry. Facial mimicry may be involved in empathy processing, and is impaired in several empathy deficit disorders. It was previously believed to follow the direct-matching principle, a theory postulating that spontaneous facial mimicry involves the observer mirroring their partner's expression exactly and automatically. However, several recent studies have demonstrated that context and individual differences may be influencing factors of spontaneous facial mimicry. At the present, it is unclear to what extent mimicry can be modulated, and thus the exact mechanisms of the mimicry and empathy relationship are still unknown. In the present study, we propose to determine the relationship between facial mimicry and empathy through measuring the EMG response of participants with high and low trait sadism. The participants will observe dynamic facial expression videos to measure their mimicry response, as well as images of limbs in painful situations to assess the specificity of this effect. EMG recordings will be measured from the corrugator supercilii, zygomaticus major, medial frontalis, and depressor angulioris. We hypothesize that mimicry does not follow the direct-matching principle, but will be altered by individual differences in trait sadism. This study will allow for a better understanding of the mechanisms of empathy, and may potentially distinguish a biomarker for disorders featuring empathic deficits.
Acknowledgements: Supported by NSERC Discovery Grant

P45

Using Meditation to Reduce Risk of Falls and Improve Attention in Older Adults: a Pilot Study

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Falls in older adults are a major healthcare concern given the resulting injuries and medical costs. Previous literature suggests that falls 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 is meditation. Meditation can be defined as regulation of the self and bringing awareness and focus to the present. Therefore, our current study examined whether using meditation training in community-dwelling older adults would improve their attention and reduce risk of falling. We conducted a four-week intervention where participants were randomly assigned to either a: 1) focused attention (FA) meditation condition, or 2) a music listening control condition three times a week. Before and after the intervention we assessed attention using: 1) the Sustained Attention to Response Task (SART), and 2) resting state EEG where we measured individual alpha peak frequency (iAPF). Mobility was measured by several assessments including the Timed Up and Go Test. Our results show a trend towards improvement in SART performance, as well as an increase in iAPF in the FA meditation group. The FA meditation group also showed a trend towards an improvement in mobility. The control group did not show any differences. These results suggest that FA meditation may increase attention in older adults, possibly decreasing their risk of falls. In conclusion, the use of FA meditation in older adults may provide an accessible intervention to improve mobility and attention.

P46

Prediabetes Accelerates Neurocognitive Decline in Older Adults

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Type II diabetes (T2D) is associated with neurocognitive decline beyond normative aging, and thus older adults with T2D are at high risk for developing dementia. However, the extent to which neurocognitive deficits occur in prediabetic older adults is not well understood. While few studies have shown that prediabetic older adults experience some cognitive decline, further research is needed to determine the specific cognitive domains affected and the degree to which this decline occurs. Moreover, structural and functional brain changes that may occur with these deficits is currently unknown in this population. Therefore, the aim of this study is to assess cognitive function and brain health in prediabetic older adults. We are conducting a cross-sectional analysis of older adults (aged 60-80) with prediabetes (fasting plasma glucose of 6.1-7.0 mmol/L) and healthy aged-matched controls, examining 1) cognitive performance, 2) functional brain activation as measured via fMRI (3T Siemens scanner) during a memory task, and 3) structural measures (e.g., whole brain volume) via T1-weighted images. Based on our cross-sectional analysis thus far (n=20), prediabetic older adults show impaired cognition (e.g., associative and short term memory, conflict resolution) associated with decreased whole brain volume, hippocampal volume, and hippocampal activation. Therefore, we conclude that older adults with prediabetes experience brain decline, and could benefit from lifestyle interventions to prevent or delay the onset of such decline.

P47

Conditioned Gaping Produced by Delayed, but Not Immediate, Exposure to Cocaine in Rats

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Cocaine abuse is accompanied by the emergence of negative affect such as dysphoria, irritability and anhedonia. Animals rapidly learn cues that come to predict the availability of cocaine, and these cues are able to elicit a negative affective state that can trigger cravings. The taste reactivity (TR) test has been used to measure negative affect by demonstrating that a taste cue paired with delayed, but not immediate, access to cocaine elicits the conditioned aversive reaction of gaping. Wheeler et al. (2008) demonstrate that multiple brief exposures to saccharin over 30 minutes, followed by a self-administration task, ultimately resulted in rats displaying conditioned gaping upon re-exposure to saccharin. They hypothesize that the aversive reaction of gaping was produced by the association of saccharin solution with an aversive state of cocaine withdrawal. However, the effect of delayed access to cocaine producing conditioned aversion to saccharin may be specific to the affective properties of cocaine, rather than the anticipation of future reward. Ettenberg (2004) suggests that while the immediate effects of cocaine are rewarding, the aftereffects (10-15 min) are aversive. Using the TR test, this research investigates whether the conditioned aversion to saccharin paired with delayed access to cocaine arises because of the mixed rewarding and aversive properties of cocaine, or if delayed access to any rewarding drug producing craving or withdrawal is responsible for the conditioned aversion to cocaine.

Supported by research grants from the Natural Sciences and Engineering Research Council (NSERC 92157) and the Canadian Institutes of Health Research (CIHR 137122).

P48

Individual MDD Patient Microbiota but Not Pooled Microbiota Induces Depressive-like Behaviour in Gnotobiotic mice

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Background: Major depressive disorder (MDD) is a common, yet poorly understood mood disorder. Recent studies have reported altered intestinal microbiota profiles in MDD patients. Additionally, colonization with pooled fecal microbiota from several MDD patients has been shown to induce depressive-like behaviour in mice. Microbiota composition and its metabolic activity greatly differ between individuals. Therefore, it is possible that pooling microbiota abrogates features

that are unique to individual donors. Here, we investigated whether the transfer of microbiota from single MDD patients or pooled microbiota from several patients could induce depressive-like behavior in germ-free (GF) mice.
Methods: GF NIH Swiss mice of both sexes were colonized with either fecal microbiota from a single donor (MDD patient 1-4or matched healthy control 1-4) or pooled fecal microbiota from four donors (all MDD patients or all healthy controls).Mouse behaviour was assessed, using the open field test, three chamber sociability assay, tail suspension test, and sucrose preference test.
Results: Colonization with microbiota from only one MDD patient induced depressive-like behaviour in mice, as assessed by the sucrose preference (anhedonia) test and the sociability assay. Behaviour did not differ between mice in the two pooled groups.
Conclusions: Colonization with pooled microbiota results in a nonspecific behavioural phenotype in recipient mice. We hypothesize that the intestinal microbiota is involved in MDD pathophysiology in only a subset of patients.

Acknowledgements: Supported by NIH.

P49

Social Instability Stress Administered Either in Adolescence or Adulthood has a Lasting Effect on Preferences for Natural Rewards in Male and Female Rats

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Rats that undergo social instability stress (SS; daily 1 h isolation+pairing with new cage partner for 16 days) in adolescence have a higher intake of sucrose (under conditions of competition) and show more social approach than do control (CTL) rats. Here, we investigated whether SS administered in adolescence (postnatal day [P] 30-45) versus adulthood (P70-85) influenced the trade-off between social preference and sucrose preference by having rats choose to spend time with an unfamiliar peer versus access to 0, 2, 5, or 10% sucrose (each concentration tested on a separate day,), and tested either days or weeks after the SS procedure relative to CTL rats. The factors of Sex, Age of SS, and Time since SS were not significant, nor did these factors interact with sucrose concentration. The Group (SS, CTL) by Concentration interaction was significant ($p = 0.002$): The preference for social was larger in SS than in CTL rats at the 0% concentration ($p < 0.001$) only. For SS rats, the preference for social decreased between 0 and 2% ($p = .028$) and between 2 and 5% ($p = .001$), and CTL rats only decreased between 5 and 10% ($p = 0.037$). In separate tests, SS and CTL rats did not differ in their preference (~56%) to spend time near an unfamiliar versus familiar peer, nor did they differ in preference (~60%) for 5% versus 0% sucrose. Thus, social instability has a lasting effect on reward systems in both sexes, and adolescents are not more susceptible than adults.

Acknowledgements: Supported by NSERC.

P50

I think therefore I can: memory self-efficacy predicts performance on memory related tasks in older adults with mild cognitive impairment

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Introduction: In our aging population, cognitive decline and the preservation of memory ability are critical areas of concern for healthy aging. Evidence has shown that personality factors such as self-efficacy, one's personal perceived ability to successfully perform a specific task, directly impacts components of healthy aging. In healthy older adults, memory self-efficacy (MSE) has been seen to be related to performance on memory tasks. However, it is unknown whether MSE might be associated with memory performance in a population already experiencing objective declines, specifically those diagnosed with Mild Cognitive Impairment (MCI).
Hypothesis: We hypothesize that memory self-efficacy will be strongly associated with performance on a battery of tasks used to assess memory ability, beyond variables that are traditionally associated with memory performance, namely age and cortical volumes.
Materials and methods: Using a cross-sectional design, community dwelling older adult women with Mild Cognitive Impairment were asked to evaluate their memory self-efficacy using the Multifactorial Memory Questionnaire (MMQ). After which they completed a series of cognitive tests, Alzheimer's disease Assessment Scale –Cognition (ADAS-Cog), Auditory Verbal Learning Test (AVLT), Sniffin-Sticks 16, and an associative memory task, to assess multiple domains of memory abilities. Using a 3T SIEMENS scanner, T1 weighted structural imaging was obtained. Multivariate linear

regression models were constructed for the four memory assessment tasks in relation to MSE measures, co-varying for age, education, Montreal Cognitive Assessment Score (MoCA), and white matter volume.
Results: We found that upon adding the scores from the MMQ to the models significant predictive value was added to the explained variance of memory performance, beyond age, education, white matter volume or MoCA score. The model for AVLT performance was the exception to this, where memory self-efficacy rating did not add to the model.
Discussion and Conclusion: Our created models are similar to other studies that have examined healthy older adults and memory performance, with memory self-efficacy adding a moderate amount (~15%) of predictive variance to the models. While our results provide support for the association between memory self-efficacy and performance in a cognitively impaired population, this study is cross-sectional and thus the directionality of this self-efficacy and performance relationship cannot be determined. However, these results provide an important stepping stone in exploring whether the training of positive memory self-efficacy could buffer the effects of declines beyond normal aging in order to maintain levels of memory functionality.

P51

Functional Characterization Following CRISPR Knockout of SWI/SNF Core Subunits in Neurodevelopmental Disorders

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Dominant *de novo* mutations are an important cause of Intellectual Disability (ID) and other neurodevelopmental disorders. Mutations in*SMARCC2* and *SMARCE1*core subunits of the SWI/SNF complex, have been linked to individuals who present with developmental and speech delay, behavioural abnormalities, and ID. However, the neurodevelopmental functions of these genes have not yet been characterized. As the primary learning and memory center of the Drosophila brain, neurons of the mushroom body can be targeted to study the *SMARCC* and *SMARCE* orthologs, *Mor* and *Bap111* respectfully. For characterization of Bap111 and Mor within the SWI/SNF complex and neurodevelopmental disorders, generating a loss of function model is needed. Due to its high conservation to the mammalian nervous system, *Drosophila* is an ideal model. My first objective is to develop CRISPR as an effective technique to knockout *Bap111* and *Mor*in *Drosophila*. I have designed gRNAs targeting *Bap111* and *Mor* for generation of transgenic flies for use in a CRISPR/Cas9 system. With these flies, my next objective is to characterize neurodevelopmental phenotypes associated with a *Bap111* or *Mor* knockout through mushroom body developmental phenotypes and courtship conditioning assays. Next, investigating the function of *SMARCC* and *SMARCE* mutations in a humanized *Drosophila* model will be important for their functional characterization. Developing CRISPR as a reliable genetic tool allows for a wide range of modern techniques to be implemented to advance our knowledge of the complex genetic causes of neurodevelopmental disorders.
Acknowledgements: Supported by Canadian Institute of Health Research.

P52

Investigating the Role of the Cholinergic System for Reactivation-induced Object Memory Updating in a New Memory Modification Task for Rats

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Memory traces are reactivated with retrieval, causing protein degradation-dependent destabilization that renders the memory labile for a distinct time frame. Reactivated memories can be erased or strengthened, but there is limited research of retrieval-induced qualitative updates. We propose that acetylcholine (ACh)facilitates memory updates, due to its established role in memory acquisition and destabilization. Perirhinal (PRh) cortex muscarinic ACh receptor 1 (M_1) agonism triggers a cellular cascade that results in the protein breakdown implicated in destabilization preceding retrieval-induced object memory erasure. M_1 receptor activation may also initiate retrieval-induced object memory updates, but it has not been systematically tested due to lack of a validated rodent model. The present study addresses this gap by developing an object memory modification task for rats. In our task, rats sample an object, and the object memory is reactivated by a re-exposure 24h later. After reactivation, rats explore an alternate empty context. On test day, rats explore the sampled objects less when they are in the same alternate context as the reactivation phase compared to a different alternate context. The object-context combination is treated as familiar only when the context is presented within 3h after reactivation. Blockade of M_1 receptor functioning with intra-PRh microinfusions of pirenzepine prevented the contextual update to the object memory, supporting our hypothesis that M_1 receptor activation is required for object memory destabilization preceding memory updates.

Acknowledgements: Supported by NSERC

P53

Activating ERB in the Paraventricular Nucleus of the Hypothalamus in Female Mice Facilitates Social Recognition

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Through binding to their estrogen receptors (ER) in the brain, estrogens are known to influence a variety of behaviours and cognitive functions. This includes mediating social recognition (SR) orthe ability to distinguish conspecifics, in as little as 15-40 minutes. One proposed mechanism for this rapid mediation of SR is through estrogens binding to their ER in the paraventricular nucleus of the hypothalamus (PVN) which mediates oxytocin (OT) production and release. OT then interacts with its receptor in the medial amygdala (MeA) allowing social recognition to occur. Recently, it was found that infusing 17β estradiol into the PVN of ovariectomized mice rapidly facilitated SR. Additionally, these facilitating effects were blocked by infusing an oxytocin receptor antagonist into the MeA. Since the PVN expresses more then one ER, we set out to determine if the rapid facilitation of SR was caused by estrogens binding to estrogen receptor β (ERβ) in the PVN. We tested this by bilaterally infusing the ERβ agonist DPN at concentrations of 50nM, 100nM and 150nMinto the PVN of adult ovariectomized CD1 mice15min prior to a 25min 'difficult' social recognition paradigm (designed so that control mice could not demonstrate SR). This allowed any facilitating effects of DPN on SR to be measured. Preliminary results indicated that the two highest doses of DPN infused into the PVN facilitated SR. These findings suggest ERβ in the PVN may play a critical role in driving the estrogen/oxytocin brain network underlying social recognition.

Acknowledgements: Funded by NSERC

P54

The Effects of Telencephalon Lesions on Zebrafish Social Behaviour

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Zebrafish are extremely social animals that benefit from observing and learning from other conspecifics. With conspecifics they form groups called shoals or schools(which is a shoal that is closely packed together and swimmingin the same direction). While this behaviour can be seen in different environmental settings, little is known about the mechanisms that influence this social interaction. On the other hand, zebrafish are unable to solve context and spatial dependent tasks when their dorsal lateral telencephalon is lesioned, this area is thought to be analogous to the hippocampus in the mammalian brain. The hippocampus is used to encode social space and social memory, thus the analogous structure in zebrafish, dorsal lateral telencephalon, might be involved with shoaling decisions. By adapting methods from articles that have completed excitotoxic brain lesions in zebrafish and forming groups from one experimental fish with four control fish, one sham fish and four control fish, and groups of five control fish, we are able to observethe effects of lesions on nearest neighbour distance, inter-individual distance, and polarization. These differences will tell us if the dorsal lateral telencephalon is involved with social behaviours and interactions in zebrafish cognition. It is predicted that lesioned fish will have difficulty interacting conspecifics, thus swim farther away from other individuals in their group and face a different way, while control groups will become tighter as trials progress.
Acknowledgements: Supported by NSERC.

P55

Using Chemogenetics to Investigate Acetylcholine-Glutamate Co-transmission by Cholinergic Interneurons

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Cholinergic interneurons (CINs) are neurons thought to be critical for information processing and modulation of the striatum. CINs co-express the vesicular acetylcholine transporter (VAChT) and vesicular glutamate transporter 3 (VGLUT3) 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 behaviours. For instance, we have found that Ach secreted by CINs contribute to the major behavioural changes that occur in mice when both VAChT and VGLUT3 are eliminated from CINs. To generate mice with an altered striatal balance of ACh and Glu release that could be remotely manipulated, we selectively eliminated VAChT or VGLUT3 in CINs that expressed an excitatory DREADD (hM3Dq).Initial characterization indicated that using a VGLUT3-Cre driver led to hM3Dq expression in CINs, but wealso found substantial ectopic expression of this DREADD in other brain regions .Nonetheless, using physiological analysis (locomotor activity) and a cholinergic sensor, we validated the functionality of the DREADDs and that they can positively influence CIN activity in the dorsal striatum. To selectively target CINs, we bilaterally implanted cannulas in the dorsal striatum of our mouse models. Preliminary experiments indicate thatselectively activating only the release of ACh from CINs appears to favour increased locomotion. Our approach allows for exquisite flexibility to test the contribution of ACh or Glu secreted by CINs for striatal-associated behaviours.

Acknowledgements: Supported by Brain Canada, CIHR, Jonathan & Joshua Memorial Scholarship, OGS, QEII

P56

Investigating the Role of Stress on Processes of Instrumental Conditioning over the Course of Two-way Signaled Active Avoidance Training in Rats

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Negative reinforcement is said to occur when a behaviour is maintained by the avoidance of an aversive event. This definition rests on the assumption that signals predicting aversive events produce a stress response, and that avoidance reduces or eliminates this negative state. However, observations of subjects trained on a two-way signaled active avoidance (SigAA) task suggest otherwise, indicating that negative stress responses initially produced by the warning signal dissipate after extensive training. So then, what are the key principles of negative reinforcement?To investigate this important form of learning, the goal of the current research was to explore the “fearless paradox”, a phenomenon commonly observed in this paradigm. Therefore, separate groups ofmale Sprague-Dawley ratswere trained on a SigAA task using different foot-shock intensities (0, 0.2, 0.4 and 0.8 mA, n=9 each) for 9 days,and were repeatedly tested for stress-induced analgesia using the hotplate test. Between days 6 and 7, animals were given a 72 hour break,avoidance wasre-tested for 2 days, and on day 9,behaviour was measured in the absence of foot-shock. The analgesic stress responsestimulated bySigAAwas measured on days 1, 3, 6, 7 and 9.This study generated two key findings. First, learning to avoid foot-shockwas associated with reduced hot-plate latencies. Second, exposure to the signal in the absence of foot-shock produced significant stress induced analgesia in animals that did not learn the task,and thiseffect not observed in animals that showed clear evidence of avoidance learning over training. Taken together, this study confirms that once learned, avoidance behaviour is not dependent on stress reduction.
Acknowledgements: Supported by NSERC.

P57

The Effect of Stressor Controllability on Social Hedonic Responses in Rats and the Impact of a Selective Serotonin Reuptake Inhibitor

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Decreased psychosocial functioning is a major deleterious feature of depression, with social anhedonia, the reduced interest in social interactions, being the most prominent facet of anhedonia. Stress contributes to the etiology and pathology of depression, but not all stressors have the same impact. In fact, it is the controllability of stress that appears linked to depression. The current study in Sprague-Dawley male rats tested whether uncontrollable stress causes social hedonic deficits, and investigated whether stress-induced social anhedonia would be selective to a serotonin reuptake inhibitor. In a Y-maze fitted with an automated tracking system, Sprague-Dawley rats underwent a two days of conditioning protocol, where adjacent compartments contained an object and a social stimulus (another male rat).The test

subjects were then exposed to either escapable, yoked inescapable or no shocks, followed 24 hours later by exposure to an empty Y-maze where a preference was determined by measuring investigation of the compartments previously paired with the object and the social stimulus. Escitalopram (0, 5 and 10 mg/kg) was administered 30 minutes after shock exposure, 1 and 5 hours before the preference test. It was found that only rats exposed to inescapable shocksdisplayed decreased investigation of the social-paired compartment. Interestingly, this effect was reversed by escitalopram. These results suggest that stressor controllability influences social hedonic reactivity, and suggest this alteration in behavior may be mediated by a hypo-functional serotonergic system.

Acknowledgements: This study was part of the Canadian Biomarker Integration Network in Depression (CAN-BIND) program (www.canbind.ca). CAN-BIND is an Integrated Discovery Program carried out in partnership with, and financial support from, the Ontario Brain Institute, an independent non-profit corporation, funded partially by the Ontario government.

P58

Behavioural and physiological alterations following exposure to chronic multimodal stress

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Chronic stress is highly implicated in the development of major depression (MDD), possibly through elevation of inflammatory cytokines such as interleukin (IL)-6, IL-1β, IL-17A and tumour necrosis factor (TNF)-α. The primary objective of the current project in laboratory rats is to explore the relationship between multimodal stress, inflammatory cytokines, and depressive-like behaviors to uncover markers of response to antidepressant treatments. Two experiments have been performed in male Sprague-Dawley rats. In Experiment 1, rats were exposed to repeated sessions of swimming stress to explore changes in swimming and immobility, behavioral indices of despair, as well as circulating levels of inflammatory cytokines. In Experiment 2, repeated swimming stress was combined with exposure to a metabolic stressor (0, 200 and 300 mg/kg 2-deoxy-D-glucose; 2DG), and impact on depressive-like behaviors, as well as circulating levels of corticosterone and inflammatory cytokines were measured. Experiment 1 indicated that multiple sessions of swimming stress induced long-lasting behavioral despair, but levels of inflammatory cytokines were not affected. In Experiment 2, the addition of the metabolic stressor significantly increased depressive-like behaviour, serum corticosterone, and serum TNF-α. The current results in laboratory rats suggest that inflammatory cytokines may play a role in depressive-like behaviors when exposure to stress is of considerable intensity and/or duration. Moreover, having established a functional protocol for inducing a significant inflammatory response to multimodal physical stressors permits further investigation into the effects of escitalopram and ketamine on behavior and physiology.

P59

G9a and Pumilio regulate thermal nociception in *Drosophila melanogaster* larvae

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When animals experience painful stimuli, they elicit an escape response that is guided by nociceptive neuronal circuitry. In the case of *Drosophila melanogaster* larvae, they curl and roll in response to thermal nociception. We have previously shown that this response is regulated by the *foraging* gene, which encodes a cGMP-dependent proteinkinase (PKG). Expression of this *foraging*geneis regulated by the histone methyltransferase G9a and the RNA-binding protein Pumilio. We hypothesized that G9a and Pumilio were each involved in regulating the thermal nociceptive escape response. Here, we used a thermal nociceptive assay and examined *G9a* and *pumilio*mutants in wild-type and *foraging* null mutant backgrounds. We found that both G9a and Pumilio areinvolved in regulating the nociceptive escape response. Furthermore, PKGappears to function downstream of both G9a and Pumilio.

P60

Social Recognition is Mediated by the G-Protein Coupled Estrogen Receptor in the Paraventricular Nucleus

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Estrogens are gonadal hormones that perform many functions throughout the body, including within the brain. Estrogens have previously been found to mediate social recognition (SR), the ability to distinguish between previously encountered conspecifics. For example, when estrogen receptors (ER) are knocked out SR is impaired, while the administration of ER agonists rapidly facilitates SR. Oxytocin (OT) is also important for social behaviours, including SR. When the OT receptor (OTR) is knocked out SR is blocked. This suggests that there may be an interplay between estrogens and OT to mediate SR, possibly occurring by estrogens in the paraventricular nucleus (PVN) binding to the ERs to facilitate OT release into the medial amygdala (MeA) which would bind to the OTR to facilitate SR. We have previously found that 17b-estradiol (E2) in the PVN rapidly facilitated SR by mediating OTR binding in the MeA, showing support for estrogens' rapid effects mediating SR by interacting with OT. In the PVN, 2 of the ERs, ER beta (ERb) and the G-protein coupled ER (GPER), are highly expressed. One or both of these receptors may mediate this estrogens/OT interplay. To determine which, a GPERagonist, G1, was infused into the PVN to determine if SR was rapidly facilitated. A rapid SR paradigm is used, where novel and familiar mice are presented, and the time spent investigating them is measured. We found that SR was facilitated suggesting GPER can rapidly mediate SR in the PVN. This also suggests that GPER is likely mediating the rapid estrogenic effect on SR in the PVN.

Acknowledgements: Supported by NSERC.

P61

Determining the Structurally Interacting Residues of the Tuberous Sclerosis Complex

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Tuberous sclerosis (TS) is an autosomal dominant disorder resulting in the development of hamartomas throughout the body, in many cases, forming tubers in the brain that can lead to conditions such as epilepsy and autism. The disorder is caused by a mutation in one of the two proteins that make up the tuberous sclerosis complex, tuberin (TSC2) or hamartin (TSC1). Despite the critical importance of these tumour suppressors in the regulation of the mTOR pathway, the specific residues allowing these proteins to interact are unknown. In this study, a collaboration computational biochemists, provided *in silico* data to possible residues that would be crucial in the tuberin-hamartin binding. Using *in* vitro methods, we test the functional output and implications of mutating these computer-derived residues. One residue, K347, on tuberin was mutated to an alanine residue to abrogate binding. Through functional assays and further proteomic analysis, the results would indicate that this residue identified by the computational models has implications to the cell that suggest the tuberin-hamartin binding is disrupted. This new bimodal approach to crucial residue identification could provide quicker identification of potential drug targets and the development of therapeutic inhibitors. Moreover, this new direction of protein-protein analysis provides a more effective way of understanding residue interactions of larger and more structural unknown proteins, such as tuberin.

Acknowledgements: Supported by NSERC and Seeds for Hope

P62

Adolescent Appetitive and Aversive Nicotine Conditioning History on Subsequent Nicotine Self-Administration in Adult Male Sprague-Dawley Rats

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While cigarette smoking is decreasing, there has been a recent dramatic increase in nicotine e-cigarette use, particularly in adolescence. Adolescent nicotine exposure in rats is more rewarding than in adults, leading to greater nicotine intake, and, in humans, is associated with greater consumption and lower quit rates. *Methods:* In adolescence (PND 28-56),male Sprague-Dawley rats are randomly assigned to groups: CS+(nicotine–shock); CS+(nicotine–banana); CS-(nicotine–shock); CS-(nicotine–banana); Shock(no nicotine); Banana(no nicotine); Nicotine(no shock/banana); Saline(no shock/banana). During conditioning, rats receive alternating days of nicotine (1.0mg/kg) or vehicle (1ml/kg saline), s.c., 5 min prior to onset of a 20 min session in an operant box. Eight random presentations of shock (0.8 mA;0.5-sec) in aversive, or banana pellets in appetitive training, are delivered on appropriate training sessions. No stimuli are presented on alternating sessions when rats receive the opposite pretreatment. After conditioning, rats are surgically implanted with jugular catheters and allowed to lever-press for 0.03 mg/kg/infusion nicotine, I.V., in adulthood (PND 70). *Results:* Preliminary data suggest adolescent aversive nicotine conditioning potentiates nicotine self-administration on an

FR1schedule in adulthood. Rats receiving equal amounts of nicotine and shock on alternating days, but never co-occurring, do not show the same enhancement of self-administration as adults. Appetitive conditioning fails to enhance intake beyond what is observed in nicotine pre-exposed rats.

P63

Activity-Regulated Cytoskeleton-associated protein(Arc) is rapidly induced by 17b-Estradiol in the dorsal hippocampus and in primary cortical cells

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Estrogenshave been shown to rapidly facilitate learning, memory, and structural changes in dorsal hippocampal neurons (i.e. dendritic spines)via non-gene transcription dependent mechanisms. Rapid protein synthesis from pre-existing mRNAs is necessary for the rapid facilitation of cognition and neuronal structural plasticity by estrogens. The Activity-Regulated Cytoskeleton-associated protein (Arc) has been implicated in memory formation as well as spinogenesis. We hypothesize that Arc may mediate estrogenic facilitation of learning and memory as well as the formation of new dendritic spines. Our results show Arc being expressed within 15 to 40 minutes of acute application of 100nM 17b-Estradiolto primary cortical cells. Further, *invivo* administration of 17b-Estradiol (100nM in a volume of 0.25uL/hemisphere) into the dorsal hippocampus of ovariectomized adult, female CD1 mice also induced Arc expression within 15 to 40 minutes. To investigate Arc's potential downstream role in 17b-Estradiol rapid facilitation of learning and memory, a short-hairpin RNA was constructed and transduced into a lentiviral vehicle for selective inhibition of Arc within the dorsal hippocampus. The shRNA construct will then be used to determine whether the Arc protein mediates 17b-Estradiol's rapid facilitation of learning and memory.

Acknowledgements: Supported by NSERC.

P64

The Role of the Granular Insula in Pavlovian Drug Discrimination with Nicotine

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The insular cortex has been shown necessary for maintenance of smoking in humans and nicotine self-administration and interoceptive learning in rats. Thus, it may be necessary for associative learning with an interoceptive nicotine stimulus. Male Sprague-Dawley rats were given bilateral lesions of the GI(AP−0.4mm, ML±4.8mm, DV-6.0mm; injector 10° divergent from vertical) with ibotenic acid (n=7) or sham lesions (n=8). During training, rats received either nicotine (0.025, 0.1, and 0.4 mg/kg) or saline (1 ml/kg)s.c. 5 min prior to onset of a 20 min session in an operant chamber. On nicotine sessions, rats had 36 deliveries of 4sec access of 0.01 ml 26% (w/v) liquid sucrose. On intermixed saline sessions, no sucrose was delivered. Dipper entry rate (goal tracking) before the first sucrose delivery and locomotor activity were the primary dependent measures. The phases of training included: discrimination with 0.4 mg/kg nicotine; extinction with 0.4 mg/kg nicotine; discrimination with 0.1 mg/kg; 0.025; and 0.4mg/kg nicotine. There was little effect of GI lesions on Pavlovian drug discrimination; sham rats showed slightly more reliable discrimination than GI rats. Locomotor activity showed a marked blunting of nicotine-induced locomotor sensitization in GI rats compared to shams across training conditions until they switched to the low 0.025 mg/kg nicotine training. Therefore, unconditioned, rather than conditioned, nicotine stimulus effects were impacted by GI lesions.

P65

The effect of repeated hypoglycemic stress in rats on blood glucose and locomotion

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There is evidence that hypoglycemia is a physiological stressor that occurs during changes in glucose metabolism. Hypoglycemic stress can negatively impact several behavioural and physiological functions including negative, depressive-like behavior in mice, and avoidance behaviour in rats. In addition, hypoglycemia is associated with neural and hormonal changes including activation of the hypothalamic–pituitary–adrenal axis (HPA axis), leading to increased levels of the stress steroids. However, it is unclear if recurrent hypoglycemia can lead to changes in behaviour and function of the HPA axis stress response over time. The current research tested the hypothesis that hypoglycemia is a stressor that

produces lasting physiological and behavioural changes. To test this, male Sprague-Dawley rats received repeated administration of the glucose antimetabolite 2-deoxy-D-glucose (2-DG; 0,100, 200 or 300 mg/kg). First, animals were separated into two groups and received the challenge dose (0, 100 mg/kg) and were tested for response of blood glucose and locomotor activity. Then, the same animals were separated into three groups that received a single injection of 2-DG (0, 200 or 300 mg/kg) each day for 10 conditioning days. During this time changes in blood glucose and locomotor activity were assessed 3 times. Finally, 10 days after the last conditioning day, animals received a second challenge dose (0, 100 mg/kg) and were tested for changes in blood glucose and locomotor activity compared to challenge 1. Results showed that 2-DG increased blood glucose and decreased locomotion during all conditioning days. Significant reduction of the glycemic response to 2-DG was observed after 5 days of repeated injections. As well, 100 mg/kg 2-DG significantly decreased locomotion during challenge 1, but not challenge 2. These results in rats demonstrates that the physiological but not behavioural effects of hypoglycemic stress can be blunted with repeated occurrence, and that lasting changes can occur.

P66

Investigating the Role of the Ubiquitin-Proteasome System in Synaptic Protein Degradation Underlying Novelty-Induced Object Memory Destabilization in Rats

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A protein synthesis-dependent process known as memory consolidation is thought to stabilize learned information into long term memory (LTM).LTM storage is more dynamic than once believed, reflecting that memories are not fixed entities. Reminder cues can reactivate and destabilize long-term memories such that they are vulnerable to modification. That said, not all memories simply destabilize. Previously, our group has shown that the destabilization of older and strongly encoded object memories requires novel contextual information at the time of reactivation. Our group has also demonstrated pharmacologically that novelty-induced object memory destabilization involves the ubiquitin proteasome system (UPS) in the perirhinal cortex (PRh), which is in line with other research suggesting that UPS mediated synaptic protein degradation is required for destabilization of fear memories. Protein degradation is thought to be the physiological correlation for memory destabilization at the synaptic level. In the present study, we have demonstrated that destabilizing object memories in the presence of contextual novelty resulted in reduction of the post-synaptic density protein, Shank 3, in the PRh in rats, suggesting that synaptic protein degradation likely underlies novelty-induced object memory destabilization. We are also investigating the molecular signals that promote the activity of the UPS in the PRh, specifically CaMKII, and it is expected that evidence from these studies will elucidate the neurobiological mechanisms by which the relevancy of LTM is maintained over time.

Acknowledgements: Supported by NSERC.

P67

The Effect of Early Life Environmental Enrichment on Cognitive Performance in C57/BL6 Male Mice

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The cognitive reserve hypothesis posits that individuals with advantaged socioeconomic conditions and related variables will be less susceptible to dementia associated with aging and neurodegenerative disorders. This can be modeled with environmental enrichment (EE) protocols, which typically provide mice with enhanced access to exercise, novelty, and social interaction. Unfortunately, such protocols do not easily enablecontrol over the enrichment received by individual animals. Thus, we created a novel EE procedure to address these issues. We assigned 10 C57/BL6 male mice to each of the four following conditions immediately following weaning at 28 days of age: Environmental Enrichment home-cage (EH), modeled after typical EE protocols; Enrichment Track (ET), in which mice ran laps on an obstacle track 6 days/week with novel obstacles daily; Exercise Control Track (CT), in which mice ran laps without obstacles; and Standard Housing (SH). After two months, we tested all mice for cognition using Object Recognition (OR) and Object Category Recognition (OCR) tasks. The novel ET procedure produced the most robust cognitive benefits, as mice in this group performed better on these object memory tasks than mice in all other groups. These effects persisted after the mice were four weeks removed

from the enrichment protocol and tested on OR again, as well as OCR 6-8 weeks later. Thus, the ET protocol provides a refined and controlled method for testing the effects of EE on cognition and may be valuable for future studies with mouse models of human disorders.

Acknowledgements: supported by CIHR

P68

Working Memory Differences between Fallers and Non-Fallers

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Falls are a major concern for older adults and their quality of life. Cognitive impairment is associated with falls in older adults; however, the electrophysiology while performing a working memory task has not been investigated. Working memory is a necessity for everyday function (walking, postural control, conversing), and the processing of a stimulus to elicit the appropriate response may lead to important insights into potential causes for falls and help us identify older adults at risk or develop future intervention strategies. The study examined differences between non-fallers and fallers in performance on a working memory task and corresponding electrophysiology. Older adults (n=38, female=23) aged 60 – 80 years (m=68.8, SD=4.7) completed two separate sessions. The first session had general demographic, mobility and neuropsychological assessments, and participants were classified as non-fallers or fallers based on their self-reported falls history over the past 12 months. The second session assessed working memory using the n-back (0-, 1-, 2-) test, while behavioural and electroencephalograms (EEG) were recorded. The EEG results showed that fallers were more impaired in processing the stimuli, with earlier latencies for the N2 ($p<0.001$) and P3 ($p<0.001$) components in comparison to non-fallers. As well, delayed peak latencies in the N2 ($r=0.507$, $p=0.01$) and P3 ($r=0.451$, $p=0.024$) components were associated with increased accuracy in the working memory task. The results showed that fallers show processing impairments in working memory compared to non-fallers.

Developmental Neuroscience

P69

Neurodevelopmental Outcomes in Infantile Hydrocephalus: an FMRI Case Study

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Ventricle dilatation, caused by infantile hydrocephalus, can lead to compression of surrounding cortical regions, which may result in an assortment of mental and physical impairments. Due to the posterior to anterior progression of infantile hydrocephalus, posterior brain regions, such as the parietal cortex, will undergo the worst extent of damage. We postulate that damage of parietal cortex caused by ventricular dilatation in infantile hydrocephalus will lead to nonverbal learning deficits, seen in school-aged children. This case study will focus on three hydrocephalus patients who were shunted within the first two years of life. We examined the functional outputs of the parietal cortex, which primarily regulates non-verbal cognition, specifically numeracy and visuospatial skills, through task-based fMRI as well as normative behavioural assessments. Cluster-based fMRI analysis was used to determine brain activation during a comparison task of numbers, faces and shapes.In the number condition hydrocephalus patients were found to have weaker activations intensities, and smaller cluster sizes when compared to healthy controls. Furthermore, hydrocephalus patients displayed general trends of lower scaled scores in non-verbal assessments of various behavioural tests (Beery VMI, WISC, and WPPSI). The findings as well as the methodology of this case study will offers new possibilities for future research using task-based fMRI a measure of pathological changes to brain functional anatomy in pediatric neurological conditions such as hydrocephalus.
Acknowledgements: Supported by CHRI (Child Health Research Institute) and BrainsCAN

P70

The Development of Synaptic Proteins the Macaque Primary Visual Cortex Across the Lifespan

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Vision, like many other brain functions, is vulnerable to the effects of ageing. Consequently, age-related visual deficits are observed in the elderly. These deficits, such as poor acuity and resolution, reflect changes that occur within the human primary visual cortex (V1). These changes are associated with reduced GABAergic signalling within V1, but recent studies implicate glutamatergic signalling. Human studies have shown that V1 experiences several developmental stages, during which the expression of both glutamatergic and GABAergic proteins is regulated. To date, it is uncertain whether these proteins are developmentally regulated in macaque V1 as they are in humans—a gap that questions the validity of this model organism. This study addressed this gap by quantifying glutamatergic (VGLUT1,PSD-95, NR1, NR2A, NR2B, GluR2) and GABAergic (Gephyrin, VGAT, CB1, $GABA_A\alpha1$, $GABA_A\alpha2$, $GABA_A\alpha3$, GAD65, GAD67) synaptic proteins in V1 of ageing macaque monkeys using western blot techniques (n = 8, 4 years – 33 years). Principal component analysis (PCA) highlighted proteins that contributed the most to variance within the data and helped create protein indices which reflected the development of macaque V1. While some indices showed similar trends to those observed in humans and non-primate animals ($GABA_A\alpha1$:$GABA_A\alpha2$, & NR2A:NR2B), others did not (Gephyrin:GAD65, & PSD-95:Gephyrin). These findings may inform studies of age-related visual deficits in macaques, as their underlying molecular mechanisms may differ from humans.

P71

Effects of Social Instability Stress in Adolescence in Female Rats on Social Interaction and Gene Expression in Social Brain Regions

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Adolescence is an important time of development of social brain regions. Social instability stress in adolescence (SS; daily 1h isolation+change of cage partner postnatal days [P] 30-45) leads to deficits in social behavior in SS rats compared with controls (CTL) in males; less is known in females. In expt1, SS and CTL male and female rats underwent a social interaction (SI) test soon (P46) or long (P70) after the SS. Irrespective of time post-stress and sex, SS rats spent less time in SI than CTL rats ($p=0.002$), although females spent less time in SI than males ($p<0.001$). Thus, these results replicated our previous findings of decreased SI after SS in males and extend them to females. In expt2, the effect on SI in females was not replicated (smaller sample). Nevertheless, SS females had higher corticosterone concentrations and lower Zif268 immunoreactive cell counts in the cingulate and infralimbic cortices after SI than did CTLs at P46 (all $p<0.01$) and did not differ from CTLs at P70. In expt3, brains were collected at P46 and P70 for RT-qPCR. Effects of SS on expression were observed for glucocorticoid receptor, mineralocorticoid receptor, and oxytocin receptor that depended on age and brain region (prefrontal cortex, hippocampus). There was effect of SS for corticotrophin releasing hormone receptor or vasopressin receptor1 at either age. These results extend our findings of long-lasting heightened responses to psychostimulants and decreased spatial memory after SS in females to show that their social development also is altered.
Acknowledgements: Supported by NSERC.

P72

Elevated Levels of Ataxia Telangiectasia Mutated (ATM) Protein in Autistic Young Human Male Fusiform Gyrus

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Idiopathic autism is associated with decreased levels of mTOR mRNA expression and abnormalities in GABA signaling, although the mechanism remains unclear. Interestingly, ataxia-telangiectasia mutated (ATM), a serine/threonine protein kinase originally thought to be associated with the DNA damage response, has been found to repress mTOR signaling and regulate GABAergic development. A high level of ATM may help explain decreased mTOR mRNA and abnormal GABA signaling in autism. Levels of ATM between autistic and control cases, however, have not yet been compared. The purpose of this study was to determine whether levels of ATM are indeed higher in human idiopathic autism samples compared to their age- and sex-matched controls. Western blots were performed on post-mortem fusiform gyrus samples from human male autistic (n=5) and control (n=6) cases between the ages of five and sixteen years. Results demonstrated that ATM levels were higher than matched controls in four out of five autistic samples, although the overall between-group difference was not significant ($p=0.113$). This observation suggests ATM may be involved in pathways underlying autism and highlights the need to study larger cohorts. More specifically, the elevated level of ATM in some cases of idiopathic autism suggests that disruptions in mTOR mRNA expression and GABA signalling may occur through ATM. A deeper appreciation of ATM's role in autism may reveal new therapeutic targets for autism, and therefore future studies confirming our results are recommended.

P73

Lactate Dehydrogenase Influences Lifespan and Long-Term Memory in Drosophila

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How cerebral energetic needs are sustained with age are poorly defined but likely influenced by the brain region and cell type. Metabolic coupling of neurons and glia has been shown in invertebrate, honey bee and fruit fly(Drosophila melanogaster), as well as vertebrate models. Glycolytic metabolism of carbohydrates results in lactate production catalyzed by the enzyme lactate dehydrogenase (LDH). Alternatively, lactate can fuel oxidative metabolism if back converted to pyruvate by LDH. Therefore, neurons may maintain energy production by glycolytically generating lactate or use lactate provided by glial cells to maintain energy production oxidatively. In vertebrates, sharing of glial generated lactate with neurons, referred to as the astrocyte neuron lactate shuttle, has been implicated in long-term memory (LTM) formation, but aging studies are lacking. Brain lactate metabolism's role in D. melanogaster memory has never been investigated. In this study we genetically altered Drosophila LDH (dLdh) expression in neurons and glia to test the impact of lactate production on LTM with aging. Endogenous dLdh in fly heads were found to be increased with age. Moreover, perturbed glial or neuronal dLdh reduced lifespan whether dLdh expression was increased or decreased. Furthermore, aged flies with neuronal dLdh expression attenuated show increased LTM compared to age-matched controls. These preliminary results suggest that Drosophila need precisely regulate brain lactate metabolism over the course of their life in order to maintain cognitive function and CNS cell survival.

P74

Executive Dysfunction and White Matter Integrity in Children with Hydrocephalus Years After Surgery

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Hydrocephalus (HYD) is a neurological condition characterized by an abnormal accumulation of cerebrospinal fluid within the ventricles of the brain, andis the most common reason for brain surgery in children. Previous research has demonstrated that infants with hydrocephalus are a high-risk group for adverse neurodevelopmental outcomes, including impairments in executive functioning (EF) skills such as goal-directed behaviour, focusing, and shifting attention (Brewer et al., 2001; Fletcher et al., 1996; Snow, 1999). The current study aims to profile white matter correlates of executive dysfunction in school-aged children with HYD through a battery of child-friendly behavioural tasks, parental reports on theBRIEF2, and diffusion tensor imaging, a useful and non-invasive MRI technique used to assess white matter pathways in vivo. We predict that white matter integrity metrics such as fractional anisotropy (FA) and mean diffusivity (MD) in frontal networks will correlate with various measures of EF, and that patients will demonstrate worse neurodevelopmental outcomes when compared to age and gender-matched controls. Preliminary behavioural results from two patients with hydrocephalus include prolonged mean response times on a size congruency task, deficits in working memory, planning, and inhibition skills, as well as a mildly elevated global executive composite score for one patient on the BRIEF2. Future work will probe measures of FA and MD for structural correlates of executive dysfunction in a larger sample of hydrocephalic children and typically developing controls.

Acknowledgements: supported by CHRI (Child Health Research Institute) and BrainsCAN

P75

The Role of Natural Killer Cells in Mediating the Effects of Viral Maternal Immune Activation on Offspring Behaviour

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Maternal infection and the associated immune response during pregnancy are known risk factors for neurodevelopmental disorders such as autism spectrum disorder (ASD) and schizophrenia in the offspring. In rodents, maternal immune activation (MIA) by pathogen-free immune stimulation in pregnant mothers produces brain and behavioral deficits in the offspring. However, the contribution of the placenta in MIA mechanisms is poorly understood. Natural Killer (NK) cells are immune cells present in the uterus and placenta and may play a role in MIA pathophysiology. We induced MIA using the viral mimic polyinosinic: polycytidylic (poly I:C) at gestation day 9.5 in either wild type (WT) rats or NK knockout rats. We hypothesized that poly I:C MIA will differentially affect offspring brain morphology and behavior in adolescence (6 weeks) and adulthood (3 months) depending on whether they are bred by WT or homozygous knockout parents. We tested the offspring in social behaviour, open field exploration and habituation and multimodal prepulse inhibition (PPI) of the acoustic startle reflex. We also sought to determine microglial number and activation at each age-point using immunostaining. Preliminary results show that startle reactivity was reduced in adolescent poly I:C offspring, whereas PPI was unaffected. Some behavioural effects seem to be absent or reversed in NK knockout rats, and further testing is in progress to account for litter effects and confirm the maternal immune response. Our results will help elucidate the role of NK cells in mediating MIA's effects on neurodevelopment.

Acknowledgements: Supported by the Jonathan and Joshua Memorial Scholarship

P76

A Developmental Survey of Immune Protein Expression in the Human Visual Cortex

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Although the brain has traditionally been considered immune-privileged, recent studies reveal that a large number of immune proteins are expressed in the healthy central nervous system. In addition to their immunological roles, these proteins regulate several key neurodevelopmental processes, including neurogenesis, neuronal migration, synapse formation, and synaptic plasticity. Current research indicates extensive communication between the immune and nervous systems, suggesting that immune proteins may mediate pathological responses to chronic inflammation in several brain disorders. Despite the important role that immune molecules play in the healthy and diseased brain, little is known about their developmental expression in the human cortex. To address this gap, we surveyed the expression of 200 immune proteins in post-mortem tissue from 30 healthy human cases covering the lifespan (20 days - 80 years, F = 12). Samples were acquired from the visual cortex, a well-characterized model of synaptic development, where previous studies of molecular development can help inform current findings. Principal component analysis (PCA) was used to highlight proteins that contributed to lifespan changes, and robust sparse k-means clustering (RSKC) revealed overlapping, age-dependent states of immune expression. In addition, biological function and cell-type specificity were explored. The current project provides novel insights into immune expression in the human cortex, and a foundation for future research investigating the role of immune processes in normal and abnormal development.

P77

The Effects of Prenatal Dexamethasone Treatment on Hippocampal Stress Sensitivity

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Dexamethasone (DEX), a synthetic glucocorticoid (GC), is often prenatally administered to aid with lung development for infants at risk of being born prematurely; however, the long-term consequences of prenatal DEX exposure on brain development are not fully understood. GCs play a prominent role in stress responses, exerting their effects by binding to the GC receptor (GR) and the mineralocorticoid receptor (MR). Under non-stressed physiological conditions, GCs primarily bind MR. GRs are activated under stressful conditions when circulating GC levels are high. The hippocampus (HPC) contains GR and MR and plays a critical role in GC-mediated negative feedback. The current study aims to determine the effects of prenatal GC exposure on HPC development and stress sensitivity, in CD1 mice. Pregnant dams were injected with 0.1 mg/kg of DEX or a sesame oil control, during mid to late pregnancy. This dose was chosen to replicate what is used to treat women at risk for pre-term labor. One week following birth, mice were sacrificed and brain tissue was collected. The HPC and overlying cortex were micro-dissected, then quantitative PCR was used to determine changes in the expression of genes that play a role in the stress response. Although GR expression was unaffected, the data suggest that DEX treatment may cause down-regulation of MR expression, in both males and females. This may cause lifelong changes in GC feedback on the brain and pose a risk factor for neurological disorders associated with altered GC sensitivity.

Acknowledgements: Supported by NSERC.

P78

Developmental stage dependent effects of embryonic alcohol exposure on the behavior and morphology of zebrafish larvae: A strain comparison study

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Despite the known deleterious effects of alcohol, Fetal Alcohol Spectrum Disorder (FASD) remains prevalent worldwide because of alcohol consumption by pregnant women. The severity and symptoms of FASD show high variability across affected children. One possibility for this variance is consumption of alcohol at different stages of pregnancy. Another is the genotype of the fetus. Zebrafish allows precise dosing and timing of alcohol delivery during embryonic development. Here we investigated how embryonic alcohol administration affected behavior and anatomy in two different zebrafish strains, AB and WT. To examine the possible differential effects of timing of alcohol exposure during embryonic development, we immersed zebrafish embryos into 1% ethanol solution or freshwater (control) for 2 hours at 8, 16, 24, 32, or 40 hours post fertilization, respectively. Subsequently, we allowed the embryos to develop normally. At 6-8 days post-fertilization, we measured the behavior of each fish singly in a Petridish during a 30-minute session, quantifying their swim

path parameters. We also measured basic anatomy features of their body and eyes. Data analysis is ongoing, but we already detected developmental stage and strain dependent alcohol effects in swim speed, turn angle and other swim path parameters, which we will report in our presentation.

P79

Early Prenatal Testosterone Reduces HPA Axis Responsiveness in CD1 Male Mice

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Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder which predominantly affects males. Testosterone (T) is elevated in the male fetus during pregnancy, where it permanently programs neuroendocrine function and behaviour. Slight elevations of prenatal T in mice affected social and anxiety behaviours, specifically in males. Thus, elevations in prenatal T have been hypothesized as a risk factor for ASD. The mechanisms behind prenatal T's effect on behaviour remain unknown. Prenatal T and glucocorticoid (GC) exposure similarly affect offspring behaviour. Thus, we hypothesized that prenatal low dose T and GC exposure might interact and exert similar effects on the developing brain. We assessed the impact of elevated prenatal T and dexamethasone (DEX; a synthetic GC) on GC levels in mice. Pregnant CD1 mice were treated with T propionate (10ug), DEX (0.1mg/kg), or sesame oil on gestational days 12, 14, and 16. Corticosterone (CORT) was measured during adolescence in hair samples, as well as in adulthood in plasma at 10 minutes, 1 hour, or 3 hours following 30-minute restraint stress. Although prenatal T had no effect on CORT levels in hair, prenatal T reduced CORT responsivity to restraint stress in males, but not in females. No effects of prenatal DEX on adult CORT responsivity were observed, in either sex. Thus, low doses of prenatal T might affect behaviour in male offspring by impairing development of the male hypothalamic-pituitary-adrenal axis. These findings may have implications for the understanding of sex differences in ASD.

Acknowledgements: Supported by NSERC.

Cognitive Neuroscience

P80

Improving Stimulus Realism: The Effect of Visual Dimension on Affective Responding

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For decades researchers have been working with two-dimensional stimuli under the assumption that these images accurately represent real objects. This assumption has been challenged by recent research which has found that two-dimensional images can evoke different neural mechanisms and receive different neuroeconomic valuations than three-dimensional objects. Our experiment series will continue this line of research in the field of affective cognitive neuroscience; a field where small effect sizes are common as brain areas related to emotional encoding rapidly habituate to two-dimensional emotive stimuli (i.e. amygdala, anterior cingulate cortex, orbitofrontal cortex). The present study uses realistic two- and three-dimensional threatening images to determine the impact visual dimension has on perception and affective responding. Based on previous research, we hypothesize that emotive three-dimensional stimuli will receive higher initial responses and be more resistant to response attenuation caused by repeated stimulus presentation than two-dimensional stimuli. The study uses subjective ratings to measure perception and psychophysiological measures (i.e. electrodermal activity and electromyography) to measure affective responding. Preliminary subjective data reveal a large effect of visual dimension; participants rate three-dimensional images as more realistic and arousing compared to two-dimensional images. Preliminary psychophysiological data show no significant difference in habituation effects between the two stimulus types.

Acknowledgements: Supported by NSERC.

P81

The Role of Learning and Memory in the Mushroom Body of *Drosophila Melanogaster*

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Intellectual disability (ID) is a neurodevelopmental disorder associated with many epigenetic regulators and chromatin modifying enzymes. Many of the known dominant ID genes are related to post – translational modifications (PTMs) which have roles in defining gene expression patterns in different cell types. Histone modifications are covalent PTMs that have been strongly implicated in the regulation of higher brain functions, like learning and memory. Here, I will systematically investigate the roles of 9 histone lysine demethylases (KDM) in learning and memory in the model organism, *Drosophila melanogaster*. The transgenic GAL4/UAS system will be used to generate shRNA that will then be processed by RNAi mediated knockdown. A tissue specific promoter will be used to target knockdown in the mushroom body (MB), the learning and memory center of the fly brain. Male flies are then tested using a well – established memory assay called courtship conditioning to test for short – and long – term memory (STM and LTM) impairment. STM is not dependent on gene transcription so defects would likely be due to developmental defects or defects may indicate a role for KDMs in memory – dependent transcriptional activation. So far, knockdown of the KDMs: Lid, UTX, and Su(var)3-3 have shown to cause memory loss while KDM4B has shown no significant reduction in memory. MB morphology will also be looked at to determine if there are defects associated with the gene knockdowns. These findings will help uncover the roles of KDMs in regulating neuronal processes and *Drosophila* memory.

Acknowledgements: Supported by Children's Health Research Institute, CIHR

P82

Distinguishing Appraisals of Memory Accuracy and Occurrence using Functional Near-Infrared Spectroscopy: a Pilot Study

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This small pilot study examined the effects of different types of social feedback on one's memory for events, specifically identifying brain activity associated with participants' response to this feedback. Participants watched 30 videos and listened to 30 audio descriptions of an actress performing tasks such as "making a sandwich". One week later, participants were given a memory recognition test, and were then provided feedback about either the occurrence or the accuracy of their memory for 8 scenes that they had correctly identified from the week prior. Functional Near-Infrared Spectroscopy was used to demonstrate that when participants receive disconfirmatory feedback about their belief in the occurrence of scenes (when told that a scene that *was* presented, was not actually presented) the associated left-hemisphere brain activity differs from when participants receive disconfirmatory feedback about their belief in the accuracy of scenes (when told that they remembered less than 50% of the details correctly).The former demonstrated a focal increase in oxygenated hemoglobin around Brodmann area 46, whereas the latter showed a more diffuse increase throughout the left dorsolateral and ventrolateral prefrontal cortex.This research shows that despite being largely synonymous metamemory appraisals in the literature, they may demonstrate more distinct underlying neurocognitive processes. These findings could influence applied fields that rely on memory reports to better distinguish between one's belief that an event occurred and belief in the accuracy of what is recalled.

Acknowledgements: Supported by NSERC Discovery Grant.

P83

The Impact of Auditory vs. Visual Emotional Cues on Visual Processing

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Emotional information has privileged access to processing resources, causing it to have either a distracting or facilitating effect on task performance for reasons that are poorly understood. Emerging evidence suggests that the sensory modality of the task-irrelevant emotional stimuli is one factor that determines the nature of the effect. Some findings suggest that auditory stimuli facilitate visual task performance while visual stimuli interfere with it, but there are conflicting findings. We hypothesize that emotional content of a different sensory modality from the task improves task performance via a general alerting and arousing effect for all stimuli. In the case of emotional content of the same modality, this effect is outweighed by increased competition for representation, resulting in an interference effect. Participants will attempt to identify the location of a symbol, either on the left or right side of a computer screen, while a negative or neutral image or sound is presented. Their reaction times will be compared across conditions. We predict that task-irrelevant emotional content presented through the auditory modality will result in faster responses compared to auditory neutral content. Conversely, emotional content presented visually will lead to slower responses compared to visual neutral content. This research will lead to a better understanding of how the way emotional information is presented can determine its effect on task performance.It will also lay the groundwork for fMRI studies delineating the neurocognitive signatures of these effects.

Acknowledgements: Supported by an NSERC Discovery Grant.

P84

Measuring the Effects of Sports-Related Concussion on Default Mode Network Activity Using Functional Near Infrared Spectroscopy

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One area of interest in current cognitive and affective neuroscience research is the default mode network (DMN), which is active when a person is at rest and is not focusing on completing a task. Research suggests that mild traumatic brain injury (mTBI), such as sports-related concussion, can negatively impact the activity of this network leading to difficulties with sustained attention and transitions between rest and activity. This study was designed to use functional near-infrared spectroscopy (fNIRS) to measure the effects of sports-related concussion on DMN activity in varsity athletes with a sports-related concussion (Mean age= 21.33, SD = 0.577; 2/3 female) and individuals without a sports-related concussion (Mean age=21.71, SD = 2.87; 5/7 female) as a control group. Participants alternated between a stop-signal task, that acted as an active trial, and a rest trial in order to engage the DMN while taking recordings from the right dorsolateral pre-frontal cortex and medial prefrontal cortex with fNIRS. Concussed participants showed higher levels of oxygenated hemoglobin in default mode network associated regions during the active task. Concussed participants also showed lower levels of default mode network activity compared to the controls during rest. This suggests concussed individuals were incompletely or inefficiently switching between DMN when at rest and the attentional network during the active trials, and vice versa.

Neurological Diseases

P85

Effect of Thermal Stress on the Intracellular Localization of Constitutively Expressed Heat Shock Protein HSPA8 (HSC70) in Cultured Human Neuronal Cells

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Heat shock protein A8 (HSPA8), also known as Hsc70, is a constitutively expressed member of the Hsp70 multigene family that is abundantly expressed in unstressed neurons. Our previous studies suggest HSPA8 may play an important role in the pre-protection of neurons from cellular stress. In comparison to the widely studied stress-inducible Hsp70 which has been a focus in cellular repair mechanisms and as a potential beneficial strategy for combating neurodegenerative diseases, constitutively expressed HSPA8 has been over looked. This study highlights the importance of HSPA8 and its role as a fast responder to cellular stress in differentiated human SH-SY5Y neuronal cells. The effect of heat shock on the intracellular localization of HSPA8 was compared in differentiated and undifferentiated human SH-SY5Y neuronal cells. HSPA8 rapidly translocated into the nucleus of differentiated neuronal cells after heat shock but not in undifferentiated cells. Members of the protein disaggregation/ refolding machine, namely DNAJB1 (Hsp40) and HSPH1 (Hsp105α), co-localized with HSPA8 at stress-sensitive sites at the periphery of the nuclear speckles where transcription takes place. The rapid targeting of constitutively expressed HSPA8 to nuclear sites suggests that differentiated human neurons are able to assemble a protein disaggregation/ refolding machine after cellular stress without the time lag needed to induce stress-inducible Hsp70.

Acknowledgements: Supported by grants from NSERC to I.R.B.

P86

Novel Genetic Signature in the Frontal Cortex of Living Patients with Parkinson's Disease

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Introduction: RNA sequencing (RNAseq) is an innovative unbiased method to define aberrant gene expression in Parkinson's Disease (PD). To date, however, RNAseq studies in PD are scant and restricted to peripheral or cadaveric tissues. Hypothesis & Objective: Living brain samples possess a more sensitive and representative genetic signature than previously studied tissues. This study sought to identify differentially expressed genes (DEG) in the living PD brain and compare this genetic profile with published RNAseq data. Methods: RNA extracted from living cortical biopsies (6 PD, 5 control patients) was sequenced on an Illumina HiSeq 2500 and DEGs identified using edgeR. Comparison of this living brain DEG dataset with reported RNAseq datasets in PD was automated with R scripts to identify highly concordant or discordant genes. Profiles of genes found in each tissue were also compared to this dataset pairwise to look for correlations between tissue types.Results:376 significant DEGs were identified in the living brain samples. Of these, 128 were not identified in any of the 7 peripheral or cadaveric tissue datasets. In contrast, a small subset appeared both in the living samples and the majority of comparative datasets. The living expression profile showed a significant correlation to SNpc and two anti-correlations. Conclusions: This pilot study revealed a unique genetic signature in living PD brain compared to peripheral or cadaveric tissues. The novel DEG profile highlights putative new biomarkers that may shed light on PD pathogenesis and warrant further investigation.

P87

Induction of Heat Shock Proteins in Differentiated Human SH-SY5Y Neuronal Cells by Caffeine and Cafestol

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Protein quality control mechanisms progressively fail during aging of the nervous system, leading to the accumulation of misfolded, aggregation-prone proteins. This triggers neuronal dysfunction and neuronal cell death, characteristic features of neurodegenerative disorders for which few effective therapies are currently available. Targeting protein quality control mechanisms is a potential treatment strategy, specifically upregulation of heat shock proteins (Hsps) that serve as a line of defense against misfolded, aggregation-prone proteins. Compounds employed in the laboratory to induce Hsps via activation of heat shock transcription factor-1 (HSF1) are toxic or exhibit bioavailability limitations in humans. Thus, alternatives are required that can be consumed regularly and cross the blood brain barrier to trigger Hsp induction in neurons that are impacted during neurodegenerative diseases. Caffeine is a non-toxic compound consumed daily that crosses the blood brain barrier. This research explores the effect of two coffee components, caffeine and cafestol, on Hsp induction in differentiated human SH-SY5Y neuronal cells. In addition to the widely studied HSPA1A (Hsp70-1), the little studied HSPA6 (Hsp70B') is investigated. HSPA6 is present in the human genome but not present in mouse and rat, hence it is missing in current animal models of neurodegenerative diseases.

Acknowledgements: Supported by grants from NSERC to I.R.B.

P88

Tuberin Regulates Cell Size via G2/M Cell Cycle Arrest

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A great deal of ground breaking work has determined that the Tuberin and Hamartin Complex function as a negative regulator of protein synthesis and cell cycle progression through G1/S. This is largely attributed to the GAP domain of Tuberin functioning to indirectly inhibit the mammalian target of rapamycin (mTOR). During times of ample nutrition Tuberin is inhibited by growth factor signaling, including direct phosphorylation by Akt/PKB, allowing for activation of mTOR and subsequent protein synthesis. It is well rationalized that fluctuation between homeostasis and cell growth requires communication between mTOR signaling and cell division, however how this occurs mechanistically has not been resolved. This work demonstrates that in the presence of nutrients, and/or Akt signaling, direct binding between Tuberin and the G2/M cyclin, Cyclin B1, is stabilized and the rate of mitotic entry is decreased. Importantly, we show that this results in an increase in cell size. We propose that this represents a novel cell cycle checkpoint linking mitotic onset with the nutritional status of the cell to control cell growth.

Acknowledgements: Supported by NSERC

P89

Cyclin B1 Increases the Expression of the Tumour Suppressor Tuberin

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Tuberous Sclerosis (TS) is a multi-systemic disorder that is characterized by benign tumours called hamartomas in areas such as the brain, heart and skin. The cause of this disease is due to inactivating mutations in either the TSC1 or TSC2 gene encoding for Hamartin and Tuberin, respectively. Mechanistically, Hamartin and Tuberin form a tumour suppressor complex, negatively regulating the mTOR pathway. Our lab has characterized how Tuberin regulates the G2/M transition through binding to and controlling the localization of Cyclin B1.We hypothesize that Cyclin B1 stabilizes Tuberin through key residues on Cyclin B1.We assessed this question through 3 aims: 1) Construct Cyclin B1 phospho-mutants using site-directed mutagenesis to determine the sites that mediate its binding to Tuberin. 2) Inhibit protein degradation through MG132 to compare protein levels and measure using western blotting techniques. 3) Immunoprecipitate Tuberin to assess the binding to Cyclin B1 compared to Tuberin protein levels.Our results show that when Tuberin is co-transfected with Cyclin B1, Tuberin protein levels are increased compared to the empty vector control.This suggests that Tuberin is stabilized by Cyclin B1. Understanding the stabilizing mechanism of this interaction not only sheds light on this critical cellular checkpoint but may also reveal novel ways to treat benign and malignant tumours.

Acknowledgments: Supported by NSERC and Seeds4Hope

P90

Cholinergic Modulation of Amyloid Plaque Deposition in Alzheimer's-like Pathology

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Cholinergic deficiency is a characteristic of many neurodegenerative disorders including Alzheimer's disease (AD), the most common form of dementia. Decreased levels of the vesicular acetylcholine transporter (VAChT) have been detected in early AD patients compared to controls, and previous work suggested that cholinergic deficiency can increase AD-like pathology in mouse models. In humans, plaque pathology has beenlinked to the loss of VAChT, however, whether changes in VAChT levels have a causal relationship with plaque accumulation is unknown. To study this aspect of AD, we crossed a humanized APP knock-in mouse carrying 3 AD-associated mutations (*App*$^{NL-G-F}$)with mice overexpressing VAChT using a BAC transgene. We analyzed the number and area populated byAb plaques in the cortex and hippocampus, as well as VAChT levels at different ages. Our preliminary results show a significant decrease in plaque area in the cortex at 2 months, but not at 3 or 6 months of age. Remarkably, we observed a sharp decrease in the levels of VAChT in *App*$^{NL-G-F}$-VAChT-BAC transgenic mice at 6 months, effectively reducing the overexpression of VAChT. Accordingly, *App*$^{NL-G-F}$ mice presented age-decreased VAChT levels at 3 and 6 months when compared to 2-months of age. Moreover, elimination of cortical VAChT increased the number of plaques in *App*$^{NL-F}$ mice, a humanized model with less aggressive pathology. These results suggest that cholinergic tone modulates plaque accumulation in a humanized AD mouse model and that plaque accumulation can interfere with cholinergic tone by modulating VAChT levels.

Acknowledgments: Supported by the Ontario Trillium Scholarship (OTS) & the Canadian Institutes of Health Research (CIHR).

P91

Assessing the efficacy of a combinatorial treatment of Ubisol-Q10 and Ashwagandha root extract as a potential therapeutic for Alzheimer's Disease

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Alzheimer's disease (AD) is the most common neurodegenerative disorder and is characterized by a devastating decline in memory as well as the progression of debilitating cognitive and psychiatric symptoms. The World Health Organization estimates that 48 million people worldwide are living with AD and that the prevalence of this disease will triple by 2050 as the aging population increases. Based on its detrimental symptoms and rapidly growing prevalence, there is an urgent need for the discovery of a treatment which effectively halts the disease progression of AD. Although the molecular mechanisms of AD are not fully understood, mitochondrial dysfunction, oxidative stress, and dysfunctional protein accumulation are known to be involved in its pathology. We have previously demonstrated that a water-soluble formulation of Coenzyme-Q10 (Ubisol-Q10), an integral part of the election transport chain, is effective in reducing various behavioural and pathological symptoms in double transgenic mouse models of AD (Muthukumaran, 2018). The root extract of Ashwagandha (Withaniasomnifera) (ASH) has been shown to be effective in the clearance of amyloid-β peptides, reversing behavioural deficits, and reducing inflammation without adverse side-effects (Sehgal et al., 2012). Using both double transgenic mouse models of AD (TgAPEswe, PSEN1dE9) and presenilin-1 mutated human fibroblast cells, we assess the efficacy of a combinatorial treatment of Ubisol-Q10 and Ashwagandha root extract in reducing AD symptoms. Data from behavioural testing and biochemical analysis will be presented.

P92

Brain Tumour Organoid (BTO) Platform as a Unique Tool in Discovery of Novel Therapy Approaches and Stratifying Treatment Regimens

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Despite significant advancements in our understanding of brain cancer biology successful treatment for the most aggressive forms of the disease such as Glioblastoma Multiforme (GBM) remains dismal and overall survival rates are among the worst. The desired high success in clinic depends on progress in personalized approaches to brain cancer patient treatment. Currently, assessment of patient- specific therapy is plagued by the lack of relevant cost- and time-effective drug screening platforms. This study brings together clinical and basic science teams to develop an innovative and powerful high-throughput Brain Tumour Organoid (BTO) platform, where low-propagated, individual patient GBM cell lines will be customized and grown as mini tumours in a dish. We will optimize the environment surrounding the tumour to mimic that in the patient and will test the response of the mini-tumour to drugs that are also given to the patient. This drug screening platform will enable researchers to test a large number of drugs alone, and in combination, to stratify best regimens for individual patients and, eventually, for patient genetic subgroups. In addition, our model will offer a unique resource to study and answer several aspects and questions related to basic biology of GBM, contributing to further discovery of potential new therapy tools.

Acknowledgements: Windsor Cancer Centre Foundation, The Cancer Research Society, Canadian Cancer Society, Brain Tumour Foundation Canada

P93

The Effects of Extracellular Tau on BDNF Expression in Human Neuroblastoma Cells

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Tau protein is abnormally hyperphosphorylated in Alzheimer's disease (AD), leading to the formation of toxic, soluble aggregates causing neurodegeneration and cognitive decline. Intracellular tau over-expression reduces expression of brain derived neurotrophic factor (BDNF)which is critical for neuronal function and for learning and memory. Pathological tau is secreted from cells in AD, andthis extracellular tau may down-regulate BDNF levels in neighbouring cells. The purpose of this work is to determine if elevated levels of extracellular tau down-regulate BDNF in human neuroblastoma (SH-SY5Y) cells. Differentiated SH-SY5Y cells and empty vector-transfectedSH-SY5Y cells were treated with conditioned medium harvested from human tau-overexpressing SH-SY5Y cells and empty vectorSH-SY5Y cells (negative control). Tau concentrations were determined by ELISA. Cells were treated for 24 hours with conditioned medium atvarying concentrations of human tau. For empty vector-transfected cells, conditioned medium was concentrated to increase natural tau concentrations to that of the over-expressing cells. BDNF mRNA levels were quantified byqRT-PCR.No significant differences were found in BDNF across groups, suggesting that low amounts of tau in the medium are not sufficient to down-regulate BDNF. However, concentrating the medium concentrated additional factors that down-regulated BDNF expression. Future experiments will co-culture tau over-expressing cells with healthy SH-SY5Y cells to examine the effects of pathological tau spreading on BDNF levels in vitro.

Acknowledgements: Supported by a grant from the Alzheimer Society of Canada to MF.

P94

The Role of Microenvironmental Landscape in GBM Progression and Therapy Resistance

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Glioblastoma multiforme (GBM) is a type of brain tumour that is categorized as having the highest degree of aggressiveness, accounting for 60% of adult brain tumours with poor prognosis. Despite extensive chemo- and radio-therapy treatments, patients' relapse. Therefore, better understanding of GBM biology is crucial to the advent of effective therapeutic interventions. The tumour niche, also known as the cancer stroma, is composed of the extracellular matrix and several types of recruited cells including fibroblasts. Fibroblasts secrete diverse molecules which were found, in other types of cancer, to contribute to the maintenance of the malignant characteristics of the tumour mass. Therefore, we hypothesize that fibroblast activation plays a crucial role in the aggressiveness and progression of GBM. We will first study the characteristics and content of the fibroblast populations in sections obtained from GL261 glioma cell line-derived brain tumours, in comparison to normal brain tissue. We will employ commercially available mouse embryonic fibroblasts to establish co-cultures with GL261 cells in-vitro. Both monolayer and 3D culture models will be utilized to study the activation and the role of the fibroblast component in the control of GBM progression and therapy resistance. In summary, my project will not only contribute to a better understanding of the mechanisms regulating the GBM microenvironment, but it will also identify potential novel treatment approaches.

P95

Investigation of the Neuroprotective Efficacy of a Novel Therapeutic with Ashwagandha Root Extract and Ubisol Q10 for Parkinson's Disease

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Parkinson's disease (PD), the second most prevalent neurodegenerative disease, causes death ofdopaminergic neurons in the substantia nigra pars compacta (SNpc). PD leads to a range of symptoms including resting tremors, postural instability, bradykinesia and rigidity. Although dopamine supplements provide symptomatic relief, there is no known preventative remedy. This study is based on findings that Ubisol-Q10, a water-soluble formulation of coenzyme-Q10, shows near-complete protection against oxidative stress-induced cell death. We have found that Ubisol-Q10 neutralizes mitochondrial dysfunction in paraquat (PQ)-exposed rats. Ethanolic root extract of ashwagandha (ASH) has also previously shown neuroprotective efficacy in maneb-PQ treated mice. We used a multidisciplinary approach to examine whether post-injury intervention with ASH and Ubisol-Q10 could halt the progression of neurodegeneration in a PQ-induced PD rat model. Our behavioural tests have shown that PQ-treated rats given Ubisol-Q10, ASH or a combination of both in drinking water have reduced motor impairment compared to control rats. Tyrosine hydroxylase staining demonstrated neuroprotection of SNpc cells in Ubisol-Q10, ASH and combination treatment groups compared to negative controls. Astroglial activation and reduced Iba-1 staining in treatment groups showed pro-survival and anti-inflammatory upregulation. Additional biochemical analysis is ongoing. Given PD's high morbidity and current concerns that its occurrence may be increasing, our research explores a novel therapeutic with promising potential.

Acknowledgements: Supported by Szecsei Family, Parkinsonian Society of Southwestern Ontario

P96

Analyzing the Role of SPY1 in Diverse BTIC (Brain Tumour Initiating Cell) Populations with Specific Cell Surface Markers

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Glioblastoma multiforme (GBM) is the most aggressive form of brain tumour with 5-year survival rates of less than 10%. Data supports that select cell populations within the tumour mass, referred to as Brain Tumour Initiating Cells (BTIC), are the drivers of GBM growth. Understanding how the driving stem cell-like cells grow and divide, and what role they play in each of the GBM subtypes, may represent novel and effective treatment strategies. This project builds on exciting data

demonstrating that a unique regulator of cell growth, termed Spy1 (or RINGO by other groups) plays a normal role during brain development, but also is found at high levels in BTIC populations in GBM. In collaboration with the Henry Ford Hospital System we obtained GBM patient lines of known genomic signatures. Based on BTIC marker expression we utilized flow cytometry, magnetic bead sorting and Fluorescent-Activated Sorting (FACS) to dissect the composition of BTIC populations. We found a strong correlation of specific marker combination within distinct GBM signatures and manipulated the levels of Spy1 to study its role in clonal expansion of select BTIC pools and determine whether the Spy1 protein is a good therapeutic target to fight BTICs driving specific subtypes of GBM.

Acknowledgements: Supported by the Brain Tumour Foundation of Canada and the Taite Boomer Foundation, Cancer Research Society, Canadian Cancer Society

P97

Implications of Tumor Microenvironment on Aggressiveness, Invasiveness, and Therapy Response in Glioblastoma Multiforme

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Glioblastoma Multiforme (GBM), which is the most aggressive type of brain cancer, is characterized by distinct changes in mechanical stress and composition of the extracellular matrix (ECM). The role of specific stressful factors has not been explored in detail due to a lack of efficient diagnostic tools in the clinical setting. In collaboration with Henry Ford Health System, we developed a project utilizing Dynamic Contrast-Enhanced magnetic resonance imaging(DCE-MRI) that can create a description of mechanicalstress properties of a tumor. By studying the expression of stress response markers such as Hyaluronic Acid (HA), we established mechanosensor signatures that correlate with DCE-MRI readings. Additionally, we know that ECM stiffness and HA signaling are mediated by receptor proteins, CD44 and Rhamm. To determine if these interactions are essential for supporting GBM characteristics, we are developing a 3D *in vitro* model implementing patient-derived brain tumor organoid (BTO) cultures to replicate and manipulate tumor progression in a dynamic, stress-controlled setting. We will knockdown CD44 and Rhamm receptors in patient GBM cells utilizing shRNA lentiviral vectors to study the impact of depletion of these receptors on stress characteristics in BTOs. Moreover, we will perform cytotoxicity assays with clinical drugs to determine the impact of CD44-/-Rhamm on therapy response. These results will evolve our understanding of the factors driving GBM progression, which may assist in designing more effective therapies for patients with this aggressive disease.

Acknowledgements: Supported by Canadian Cancer Society and Seeds for Hope

P98

The Retrograde Transport of BDNF and Pro-NGF Diminishes with Age in Basal Forebrain Cholinergic Neurons

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Profound and early basal forebrain cholinergic neuron (BFCN) degeneration is a hallmark of Alzheimer's disease (AD). BFCNs depend for survival and function on neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) which are retrogradely transported from BFCN target tissues. In AD, NGF-immunoreactive material is found at abnormally high levels in BFCN targets like cortex and hippocampus and is reduced in basal forebrain, suggesting dysfunctional retrograde axonal transport of neurotrophins. Age is the greatest risk factor for developing AD, yet the influence of age on BFCN axonal transport is poorly understood. To model aging, E18 rat basal forebrain or cortical neurons were cultured in microfluidic chambers for 3 weeks. Neurons were assayed after either 7 or 18 days in vitro. To confirm an aging phenotype, cells were stained for senescence-associated beta-galactosidase (SaβG) at both time points. Quantum dot-labeled BDNF or proNGF were added to the axon terminals. DIV7 BFCNs displayed robust BDNF and proNGF transport, which diminished with in vitro age. BDNF transport did not diminish with age in cortical neurons. Significant SaβG staining was observed in aged BFCNs but not in cortical neurons cultured for 18 or more days in vitro. These results strongly suggest a vulnerability of BFCNs to age-induced retrograde transport deficits. BFCNs' unique susceptibility to age-induced retrograde axonal transport impairments, coupled with their reliance on neurotrophin transport, may explain their vulnerability to age-related disorders like AD.

Acknowledgements: Supported by an OGS scholarship to AS and grants from CIHR and the Alzheimer Society of Canada to MF.

P99

Investigating the Neuroprotective Role of Caenorhabditis Elegans MANF Homolog

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The Mesencephalic Astrocyte derived Neurotrophic Factor (MANF) is a protein from a novel family of neurotrophic factors which has neuroprotective and neurorestorative effects in mammalian models' of Parkinson's disease, however its mechanism is not fully understood. MANF is shown to have a role in the endoplasmic reticulum unfolded protein response (ER- UPR). Using the model organism C. elegans I am investigating the function of MANF using a deletion allele of manf-1, tm3603. A previous graduate student in our lab has shown that manf-1(tm3603) worms carry a 204 bp deletion replaced by a random 21 bp insertion resulting in low level MANF production. Furthermore, manf-1 mutant animals were found to have increased ER stress and accelerated degeneration of dopaminergic neurons. Using RT-QPCR I found that MANF levels are several fold lower in day 1 tm3603 mutants in comparison to wildtype. Currently I am testing mutant manf-1 worms with different ER stress inducing chemicals such as Tunicamycin and Paraquat monitoring the degeneration of the dopaminergic neurons in the cephalic region of C. elegans, examining them starting from day 1 to day 9 adult stages using Normarski fluorescence microscopy. The dendrites are being compared with wildtype neurons. It is expected that the degeneration seen in chemically-treated neurons would correlate with the lower MANF levels present in tm3603 worms. This work thus far is the beginning of a bigger story to fully understand the mechanism of MANF and its neuroprotective role.

Behavioural Neuroscience Additional Poster

P100

High-Dose Nicotine Exposure in Adolescent Rats Results in Impaired Short-Term Memory and Increased Nicotinic Reinforcement as Adults

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Adolescent nicotine exposure is an increasing concern with the emergence of electronic cigarette devices (e.g. vaping), highlighting the importance of considering long-term behavioral consequences of adolescent exposure. Male Sprague-Dawley rats (n=16, 8/group) were treated daily with 1.0 mg/kg subcutaneous nicotine or 1.0 mg/kg subcutaneous saline from post-natal days 28-42. Upon adulthood, rats underwent behavioral assessments: object recognition memory, conditioned avoidance response (CAR), and intravenous nicotine self-administration. Adolescent nicotine-treated rats displayed a significant, but selective, impairment of short-term memory (5-minute delay). A significant within-animal delay by drug interaction ($F(1,14)=4.748$, $p=0.047$) was observed; between-group analyses showed that nicotine-treated animals displayed significantly decreased discrimination ratio compared to vehicle-treated animals ($p=0.011$). No group differences were observed in acquisition or extinction of CAR. For nicotine self-administration (0.023 mg/kg/infusion), there was no effect of nicotine pretreatment on a fixed ratio 1 schedule. However, during a fixed interval 1 schedule, rats pretreated with nicotine self-administered nicotine more than rats not pretreated with nicotine [Session x Group Interaction: $F(7,70)=2.403$, $p=.029$]. Adolescent exposure to high-dose nicotine produces long-lasting changes in short-term memory and nicotine reinforcement in adulthood, underscoring the need for understanding the long-term consequences of nicotine use in adolescence.

Author Index

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