The Canadian Association
for Neuroscience presents

11th Annual Canadian Neuroscience Meeting 2017

Abstract Booklet

May 28–31, 2017

The Hilton Bonaventure Hotel
Montréal, Québec

CAN-ACN

CANADIAN ASSOCIATION FOR NEUROSCIENCE
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Table of Contents

Plenary and Keynote Abstracts

Sunday, May 28, 2017

Presidential Lecture

LINDA BUCK, Fred Hutchinson Cancer Research Center
Deconstructing Smell

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The sense of smell allows mammals to perceive a multitude of environmental chemicals as having a distinct odor. It also mediates the detection of pheromones and predator odors that elicit innate responses. We are interested in how the olfactory system detects different chemicals and how the nervous system translates those chemicals into diverse perceptions and behaviors. Using a combination of molecular, cellular, and genetic approaches, we have identified families of receptors that initially detect odorants and pheromones in peripheral sense organs, asked how those receptors encode the identities of different chemicals, and investigated how the signals they generate are routed and organized in the nervous system to yield distinct perceptions and instinctive responses. Our work also touches on other neural circuits that affect emotions and innate drives that modulate behavior.

Monday, May 29, 2017

Plenary Symposium 1

Growing, wiring and refining neural circuits in the developing brain

Chair: **Edward Ruthazer**, McGill University

KARUN SINGH, McMaster University
Signaling mechanisms regulating neural circuit formation and their relevance to neurodevelopmental disorders

The development of the mammalian brain requires precise formation of synaptic connections between neurons, and abnormalities in this process are thought to play a central role in the pathophysiology of autism spectrum disorders (ASDs). Signaling cascades, including multiple kinases, play key roles in initiating, promoting and stabilizing the growth of synapses in the cerebral cortex. We are interested in identifying novel signaling molecules and mechanisms that regulate this process with a specific goal to determine if disruption of these pathways is implicated in neurodevelopmental disorders. Our work focuses on understanding how a member of the MAP serine/threonine kinase family signals to regulate excitatory synapse development and maturation. We have identified that KO mice have multiple abnormalities in synapse development and excitatory neurotransmission in the cortex, leading to learning and memory, and social deficits. Our recent work has also identified novel mutations in this molecule from subjects with Autism. Testing of the mutations reveals they impair kinase activity, leading to abnormal development of dendritic arbors and synapses. This demonstrates that clinically-derived mutations have a detrimental impact on neurodevelopment. In addition, we have recently begun to

examine the effects on a human in vitro KO model of neurodevelopment. Together, our data describe how specific members of the MAP kinase family regulate dendritic and synapse development, and provide novel insight into the molecular mechanisms of neurodevelopmental disorders.

JULIE LEFEBVRE, Sickkids Hospital
The Protocadherin cell-surface code promotes the wiring and survival of inhibitory interneurons into brain circuits.

In many brain regions, inhibitory interneurons migrate over long distances and integrate into neural circuits with highly specific patterns in their distribution, number, and synaptic targeting. We know little of the molecular cues that coordinate local interactions for wiring of interneurons. We propose that the clustered Protocadherins (Pcdhs), a large family of cell-surface molecules, promote the morphogenesis and survival of inhibitory interneurons by mediating cell-cell interactions with target cells in developing brain circuits. The clustered Pcdhs comprise ~60 cadherin-related transmembrane proteins with an extraordinary potential for cell-surface diversity and wiring specificity. Pcdh isoforms have been shown to be combinatorially expressed among individual neurons and to engage homophilic interactions. With properties that greatly amplify cell-surface diversity and selectivity, Pcdhs are proposed to serve as a code of 'neuron individuality' to mediate complex patterns of connectivity. Our previous work in the mouse retina revealed roles for Pcdhs in dendrite self-avoidance and interneuron survival during circuit formation. Here, I will discuss our recent findings on the roles for Pcdhs in the development of GABAergic inhibitory cells in the brain. Juvenile mice lacking Pcdhs from broad classes of GABAergic cells exhibit dramatic motor deficits, anxiety, and epileptic seizures. I will discuss ongoing work in which we focus on cortical and cerebellar circuits to elucidate how Pcdhs regulate dendritic and axonal patterning and promote the survival of inhibitory interneurons during circuit formation. These studies could yield new insights on the local interactions and molecular cues required for proper establishment of inhibitory cells into circuits.

GRAZIELLA DICRISTO, Université de Montréal
Mechanisms of refinement of cortical GABAergic circuits

Within the forebrain, GABAergic (γ-aminobutyric acid producing) interneurons possess the largest diversity in morphology, connectivity, and physiological properties. Cortical GABAergic circuit development is a prolonged process that extends well into adolescence. The maturation of GABAergic connectivity is activity-dependent and, in turn, it affects neuronal circuit refinement during postnatal period of heightened plasticity. One of the most prominent classes of cortical GABAergic cells are the parvalbumin (PV)-positive interneurons, which specifically target the soma and proximal dendrites of pyramidal cells, hence the name of "basket cells". PV cells can adjust the gain of integrated synaptic responses and have been implicated in synchronizing the firing of neuronal populations and in generating gamma oscillations, which are important for perception, selective attention, working memory and cognitive control in humans and rodents. Importantly, PV cells have also been involved in experience-dependent refinement of cortical circuits during postnatal development, or critical period plasticity.

Featured Plenary Speaker

HOLLIS KLINE, The Scripps Research Institute
Building circuits to process visual information

Visual experience is essential to establish functional connectivity throughout the visual system, however the mechanisms by which activity influences neuronal development and circuit connectivity are not clear. Using Xenopus tadpoles we have identified the cellular and molecular effects of visual experience on topographic map formation, on tectal cell development and on development of the visual circuit. Dr. Cline will present results of in vivo imaging experiments demonstrating novel cellular mechanisms by which experience controls visual circuit plasticity and function.

Tuesday, May 30

Plenary Symposium 2

Glia and brain function

Chair: **RICHARD ROBITAILLE**, Université de Montréal

Glial Mismanagement of Neuromuscular Junction Structure and Function in Amyotrophic Lateral Sclerosis

A major pathogenic events in Amyotrophic Lateral Sclerosis (ALS) is the destruction of neuromuscular junctions (NMJ) leading to an extended denervation and retraction of the nerve terminal at the NMJ. Despite the importance of NMJ malfunction and the reported involvement of other glial cells in ALS, the contribution of Perisynaptic Schwann cells (PSCs), glial cell at the NMJ, remains unknown. PSCs influence synaptic efficacy, structural stability and integrity and repair of the NMJ. Interestingly, these roles are complementary and muscarinic receptor (mAChR) activation represents a central element for appropriate PSC responses. In particular, PSCs muscarinic signaling must be reduced for NMJ morphological plasticity and repair to occur. We tested whether PSC properties are not compatible with NMJ plasticity and repair and that restoring PSCs activity would rescue NMJ structure and function.

We used soleus nerve-muscle preparations of a mouse model of ALS carrying the SOD1G37R human mutation. We combined morphological and physiological approaches to determine the properties and activity of the synaptic and glial components at the NMJ. We observed that the PSCs muscarinic signaling is enhanced in a SOD1 mouse model, suggesting that their contribution to NMJ repair and remodelling in ALS would be impaired. To test this possibility, we performed chronic in vivo blockade of PSC mAChRs (using fluorescent pirenzepine, flPir) and examine whether NMJ repair was restored. Muscarinic activation of PSCs was reduced by the in vivo treatment although synaptic properties remained unaffected. Importantly, reduction of PSCs mAChRs activity restored their ability to repair and maintain NMJs structural integrity as indicated by the increased PSCs process extensions, sprouting events of the presynaptic terminals and poly-innervated NMJs.

These results suggest that reducing PSCs mAChRs activation could be beneficial in a context of ALS. This intrinsic PSC property could represent an important and novel therapeutic target in ALS.

MARIE-ÈVE TREMBLAY, Centre Hospitalier de l'Université Laval
Microglia-synapse interactions in health and disease

Discoveries spanning the last decade have challenged our view of microglia, the brain's immune cells, showing their essential but previously unexpected contribution to the experience-dependent remodeling of neuronal circuits. In this emergent field of investigation, my research aims to determine how this newly defined fundamental mechanism could be implicated in the loss of synapses that best

correlates with the impairment of learning and memory across chronic stress, depression, schizophrenia, aging, and Alzheimer's disease. In my presentation, I will discuss about our recent characterization of a microglial phenotype that is induced by chronic stress, fractalkine receptor deficiency, aging, or Alzheimer's disease pathology. These 'dark' microglia appear extremely active, even more than the normal microglia, typically reaching for synaptic clefts, while extensively engulfing axon terminals and dendritic spines. In addition, our recent findings revealed the occurrence of these dark microglia in a schizophrenia mouse model induced by prenatal immunological challenge, as well as in normal early brain development, two conditions where synaptic pruning is exacerbated. These findings indicate that dark microglia could represent a subset of cells that become stressed as a result of their hyperactive involvement with the remodeling of neuronal circuits across development, plasticity, and disease.

GRANT GORDON, University of Calgary
Behavioral State Dependence of Cortical Astrocyte Ca2+ Signals During Neurovascular Coupling

PV cell function relies on their pattern of connectivity: they innervate hundreds of postsynaptic targets with multiple synapses clustered around the cell body and proximal dendrites. The establishment of mature innervation by a single PV cell requires several steps, from finding the right cell target and selecting the appropriate subcellular location for synapse localization, to synapse proliferation and refinement. Here, I will discuss some of our recent findings regarding the molecular mechanisms regulating the timing of maturation of PV cell connectivity in the postnatal rodent cortex.

Featured Plenary Speaker

DWIGHT BERGLES, John Hopkins University
Multi-scale analysis of astrocyte activity in the mammalian brain

Understanding how information processing in neural circuits is influenced by brain state requires in vivo assessments of population activity during different behaviors. To define the mechanisms responsible for activating astrocyte networks in the adult brain, we developed conditional GCaMP mouse lines and performed in vivo two photon imaging in awake animals. Our studies indicate that there are two functionally distinct, but interdependent modes of calcium signaling in astrocytes – one based on activation of metabotropic receptors and another that is intrinsically generated. I will describe the contexts in which these modes of signaling occur and the mechanisms responsible.

Keynote Lecture

CHARLES BOURQUE, McGill University
Control of body hydration by heat, salt and circadian time

Defects in body hydration are common causes of neurological symptoms associated with acute and chronic pathological conditions. Although behavioral (thirst, salt appetite) and physiological responses (renal handling of salt and water) that maintain hydration are known, it is less clear how the brain orchestrates these to achieve homeostasis. Bourque will describe recent cellular-molecular studies revealing how hypothalamic “osmoreceptor” neurons monitor body hydration and control homeostatic effector neurons via synaptic mechanisms. The talk will also highlight feed-forward circuits can mediate

anticipatory adjustments in the absence of altered hydration, thus challenging the notion that fluid homeostasis relies mainly on negative feedback.

Wednesday, May 31

Plenary Symposium 3

Memory and Cognition

Chair: **PAUL FRANKLAND,** University of Toronto

KARI HOFFMAN, York University
Multiple roles of the primate hippocampus in visual exploration

The hippocampus plays a role in memory across various species, though species differences appear on closer examination of the tasks and neuronal correlates. I will describe hippocampal activity during learning and memory in primates as contrasted with better-established correlates in rodent models. Using this comparative lens, I will revisit the role of the hippocampus in navigation and in memory, presenting new results from memory-guided visual exploration and during wireless recordings in freely-behaving macaques

KATHERINE DUNCAN, University of Toronto
Memory States in the Human Brain and Behaviour

The key characteristic distinguishing memory from other cognitive processes is that memory's ultimate success depends on multiple phases: encoding new memory traces; storing and consolidating those traces; and retrieving the stored content. The distinct, and potentially incompatible, demands of each phase may present challenges for specialized memory systems like the hippocampus. One way that the hippocampus has been proposed to overcome these challenges is by dynamically shifting its processing to favour memory encoding in novel contexts and retrieval in familiar ones. Our research has explored this possibility, identifying evidence for hippocampal processing shifts in humans. Using fMRI, we have characterized how the hippocampus detects novelty and how novelty detection can shift connectivity along hippocampal pathways. We have also used this hippocampal framework to make new predictions about how novelty and familiarity shape memory behaviour. Specifically, drawing on the time-course of hippocampal cholinergic modulation, we have identified that recent exposure to novelty elicits a memory state that facilitates the formation of distinct memories, whereas recent exposure to familiarity facilitates the reactivation of other, unrelated associations. Together, this work highlights that memory success can depend on the state of hippocampal processing, in turn influenced strongly by the context in which the memory is made and, later, retrieved.

PAUL FRANKLAND, University of Toronto
Identification and interrogation of a fear memory network

Long-term memories are thought to depend upon the coordinated activation of a broad network of cortical and subcortical brain regions, but within this distributed network some regions may play more important roles than others during consolidation. Previously, we used a global mapping approach to identify networks of brain regions activated following recall of long-term fear memories in mice (Wheeler et al [2013] PLoS Comp Biol). Expression analysis of the activity-regulated gene, c-fos, across

84 brain regions allowed us to identify regions that were co-active following memory recall, and presumably form a network that is engaged by long-term memory recall. Graph theoretical analysis of this network indicated that the memory network had small-world properties, and included several highly-connected hub-like regions that may play privileged roles in memory expression. Using pharmacogenetic neuronal silencing strategies, here we test the hypothesis that these hub regions play disproportionately important roles in the consolidation of long-term contextual fear memories. To do this we virally expressed the inhibitory designer receptor exclusively activated by designer drugs (DREADD) HM4Di in different hub and non-hub regions in the memory network. DREADDs are insensitive to endogenous ligands but activated by a synthetic ligand clozapine-N-oxide (CNO). When bound to CNO, this Gi-coupled DREADD induces membrane hyperpolarization and inhibition of spiking activity. Following contextual fear conditioning training, CNO or vehicle was administered via drinking water for 14 days and then contextual fear memory was tested. We found that inhibition of several cortical and subcortical hub regions disrupted consolidation of the contextual fear memory. In contrast, our data indicate that similar inhibition of non-hub regions in the memory network had no effect. These data support the idea that highly-connected hub regions play a disproportionately important role in the consolidation of contextual fear memories.

Featured Plenary Speaker

TIM BUSSEY, Western University

How is memory organized? Memory Systems versus the Representational-Hierarchical View

The predominant paradigm in cognitive and behavioural neuroscience assumes that the brain is organized into processing modules specialised for particular psychological functions. With respect to memory, the textbook view is that different systems are specialised for processing underlying specific types of memory. For example, there is thought to be a memory system localised in the medial temporal that is specialised for declarative (explicit) memory. Structures in the ventral visual stream, on the other hand, are important for other functions such as perceptual discrimination, categorization, etc — the so-called "perceptual representation system". In my talk I will describe, and provide evidence for, an alternative framework – the Representational-Hierarchical View, which suggests that instead of labeling different areas of the brain as being important for different types of memory processing, it may be more useful to think in terms of content, i.e., the specific representations that different regions maintain, and specifically how higher-level representations disambiguate behaviourally ambiguous lower-level representations. This view can account for everything the memory system view can account for -- and much that it can’t.

Parallel Symposia Abstracts

Symposium 1:

Sleep mechanisms and functions

Chair**: VALERIE MONGRAIN**, Université de Montréal

Overview:
Sleep is an essential behavior regulated by complex interactions at the molecular, cellular and circuit levels. Recent technological advances in neuroscience have allowed an increasingly precise understanding of how these different levels contribute to the regulation of sleep and wakefulness and to the generation of brain rhythmic activity during the different behavioral states. The first two talks of the symposium will detail newly identified contributions of specific neuronal circuits in the control of arousal and of the different stages of sleep. In addition, behavioral state determines how the brain processes and stores information, and sleep loss impacts a variety of brain functions through intricate molecular mechanisms. The last two presentations of the symposium will be presenting, for different brain regions, how networks are impacted by sleep loss to modulate neuronal functions.

Speakers:

John Peever, University of Toronto
Circuits controlling REM sleep in health and disease

REM sleep is characterized by cortical activation, muscle paralysis and vivid dreaming, but the neural circuits that generate REM sleep remain poorly understood. Understanding the brain mechanisms that control REM sleep requires the identification of key neurons in the control circuits and mapping of their synaptic connections. Recent technical advances (optogenetics) are facilitating the identification and dissection of the circuit control of REM sleep. This talk will highlight recent advances in the interrogation of the brainstem circuits that generate REM sleep and how breakdown in these circuits underlies common neurological disorders such as narcolepsy and REM sleep behavior disorder.

Barbara E Jones, McGill University
Arousal systems and their regulation by sleep

Arousal systems include neurons distributed through the core of the brainstem, hypothalamus and basal forebrain and include glutamatergic together with GABAergic effector neurons, which through ascending projections stimulate cortical activation and descending projections stimulate behavioral arousal with postural muscle tone. These neurons commonly discharge at their highest rates during active or attentive waking and their minimal rates during sleep. They are generally excited by input from widely projecting neuromodulatory systems, including cholinergic, noradrenergic and orexinergic neurons, also constituents of the arousal systems. All of these wake-active neurons are homeostatically regulated, such that following enforced waking with sleep deprivation, when they would remain continuously active, they are submitted to homeostatic down-scaling by an increase in inhibitory receptors, which is associated with increased sleepiness and sleep drive. These changes are alleviated with sleep recovery and rebound which allows return to baseline stable levels of receptors and activity.

Emma K O'Callaghan, Université de Montréal
Contribution of circadian components to sleep homeostasis

Synaptic adhesion molecules (SAMs) are involved in the regulation of synaptic plasticity, and the formation of neuronal networks. Our lab has shown specific SAMs that are involved in sleep homeostasis, the regulation of EEG parameters, the distribution of sleep, and the recovery response to SD. We aim to uncover how the expression of these SAMs is regulated, and have identified components of the circadian clock that may modulate the transcription of these synaptic elements. In particular, we describe precise mechanisms by which elements of the circadian clock regulate the transcription of the SAM Neuroligin-1. Further, we describe that a regulator of clock transcription factors, Glycogen Synthase Kinase 3 Beta (GSK3-B) is involved in the regulation of sleep homeostasis. This presentation will elaborate upon these findings, and present novel unpublished work obtained from both in vitro and in vivo experiments, including the application of cutting-edge technologies such as CRISPR/Cas9. We will describe how these molecules may serve as a molecular link between the circadian and sleep homeostatic mechanisms.

Robbert Havekes, University of Groningen
The tired hippocampus: insight into the molecular origins of hippocampal memory deficits associated with sleep loss

Sleep deprivation (SD) is common in modern 24/7 society. Loss of sleep negatively impacts brain function and particularly affects cognitive processes requiring the hippocampus. Despite decades of research, mechanisms by which SD impacts cognition remain to be defined. We show in mice that SD decreases the number of dendritic spines in the hippocampus, which is paralleled by increased activity of the F-actin severing protein cofilin, and that recovery sleep restores hippocampal spine numbers and cofilin activity. Viral suppression of cofilin function in hippocampal excitatory neurons prevents this loss of dendritic spines, reverses the deficits in hippocampal synaptic plasticity (LTP), and impairments in long-term memory caused by SD. The elevated cofilin activity observed after SD is caused by the cAMP-degrading phosphodiesterase isoform PDE4A5, which hampers cAMP-PKA-LIMK signaling. Viral suppression of PDE4A5 function prevents changes in LIMK and cofilin signaling as well as the cognitive deficits associated with SD. This work demonstrates that alterations in structural plasticity in hippocampal neurons contribute to the deficits in synaptic plasticity and memory caused by SD.

Symposium 2:

Critical Mediators of Pain: Uncovering Novel Therapeutic Targets

Chair: **MICHAEL HILDEBRAND**, Carleton University

Overview:
Chronic pain is a major public health challenge that affects one in five Canadians and is often severe, debilitating and exceedingly difficult to treat. Current treatments provide moderate pain relief and have many side effects, as exemplified by the tolerance and withdrawal associated with opioids. Thus, there is an urgent need to identify therapeutic targets based on new mechanisms. The spinal cord and intervertebral discs in the spine are potential sites of action for new therapeutic approaches, and spinal

neuroplasticity and intervertebral disc degeneration are both associated with chronic pain. This session will highlight current research aimed at identifying the molecular players in spinal hyperexcitability and in intervertebral disc degeneration. We will discuss the roles of specific receptors, channels, intracellular signaling pathways, and epigenetic mechanisms in mediating pathological plasticity and degeneration. Based on evidence from ex vivo assays, rodent models of pathological pain and human pain conditions, we will discuss how targeting these diverse mechanisms reverses pain-related pathologies ranging from opioid tolerance to neuropathic and low back pain.

Speakers:

Daniela Salvemini, Saint Louis University School of Medicine
Deregulation of adenosine signaling at the A3 adenosine receptor subtype drives chronic neuropathic pain states - new insights in a novel therapeutic target.

Chronic neuropathic pain affects 15-20 millions of individuals in the US alone. Neuropathic pain conditions are chronic, often severe, debilitating and exceedingly difficult to treat. People with neuropathic pain also often have depression, sleep disorders and anxiety greatly impacting the quality of life of the patient. Current treatments provide moderate pain relief and have many side effects as exemplified by the use of opioids. There is an urgent need to identify therapeutic targets based on new mechanisms. Our recent work suggests that deregulation of adenosine signaling at the A3 adenosine receptor subtype contributes to the development of chronic neuropathic pain syndromes and to opioid unwanted actions such as analgesic tolerance and increased pain sensitivities. Building on these findings our work led to the discovery of selective A3AR agonists as potent non-narcotic analgesics for the management of chronic neuropathic pain. I will give an overview of our recent findings in this area.

Michael Hildebrand, Carleton University
Molecular determinants of dorsal horn hyperexcitability in pathological pain processing

To effectively target pathological pain processes, the molecular changes that mediate spinal dysfunction need to be identified. Hyperexcitability within the dorsal horn of the spinal cord results from a disruption in the balance between excitation and inhibition, leading to increased pain transmission from lamina I dorsal horn neurons to the brain. We have recently found that excitatory NMDA receptors at lamina I synapses are potentiated following peripheral nerve injury or inflammation. We find that BDNF mediates this potentiation of synaptic NMDAR responses through activation of TrkB and the Src-family kinase, Fyn. Surprisingly, we also find that chloride-dependent disinhibition is necessary for the potentiation of NMDARs. In rodent and human models of spinal pain pathology, we find that the phosphatase STEP61 is the molecular brake in lamina I neurons that is lost to connect these two distinct pathological mechanisms. Importantly, blocking this feed-forward spinal mechanism reverses inflammatory pain hypersensitivity. Thus, we propose that targeting specific molecular determinants of spinal pain amplification is a potential therapeutic approach for treating pathological pain.

Laura Stone, McGill University
Preventing pain at the source: targeting intervertebral disc degeneration as a therapeutic strategy for low back pain.

Intervertebral disc degeneration is a major cause of chronic low back pain. The pathological mechanisms underlying painful disc degeneration, including pathological innervation and inflammation, are therefore potential targets for new therapeutic approaches. Recent evidence implicates multiple molecular targets

including toll-like receptors (TLRs), neurotrophins and cytokines in disc degeneration and low back pain. Studies indicating a role for TLRs, neurotrophins and cytokine production in human disc pathology will be presented along with in vivo data demonstrating the therapeutic efficacy of targeting each these pathways in a pre-clinical model of low back pain and disc degeneration. Together these studies support the idea that targeting pain at its source by inhibiting disc degeneration is a viable therapeutic strategy for back pain.

Symposium 3:

Control of locomotor activity: from the cortex to the spinal cord

Chair: **SIMON GOSGNACH**, University of Alberta

Overview:
Locomotion is an essential motor act which is characterized by the rhythmic alternation of muscles on the left and right sides of the body. This rhythmic activity is generated by a neural circuit located in the spinal cord (the locomotor CPG) which receives inputs from the cortex and the periphery in order to tailor its activity to accommodate environmental cues. Recently, much has been learned about component interneurons of the locomotor CPG, however we still know little regarding the manner in which sensory and descending input interface with it, and fine tune its output. In this symposium we will discuss new findings regarding the connectivity of genetically defined interneuronal components of the locomotor CPG, and the manner in which activity of these interneurons is modulated by sensory afferents. We will also discuss how cortical and subcortical areas are involved in the planning and modulation of locomotor activity based on sensorimotor cues. The overarching goal of this symposium is to begin to unravel the complex connectivity between components of the CNS that interface with the locomotor CPG and enable purposeful, goal directed locomotion to be generated.

Speakers:

Trevor Drew, Université de Montreal
Walking 101 : What the brain tells the spinal cord.

Cortical and brainstem structures play a critical role in the control of locomotion, ensuring that gait is appropriately modified to account for any changes in the environment. Critical functions of supraspinal structures include: control of posture; step-by-step regulation of the level of muscle activity; precise modifications of gait to adapt to obstacles in the environment; and the advance planning of gait changes on the basis of vision. Each of these functions is primarily regulated by different regions of the brain, albeit with varying degrees of overlap. The control of posture and the step-by-step regulation of locomotion, for example, is regulated primarily by structures in the brainstem while the motor cortex contributes primarily to the execution of the precise gait changes required to negotiate obstacles under visual guidance. There is less information on the planning of gait modifications but recent evidence suggests that the posterior parietal cortex, the premotor cortex and the basal ganglia contribute to an estimation of object location and to limb selection. Together these diverse signals provide the flexibility required to negotiate a complex environment.

Patrick Whelan, University of Calgary

Parallel dopaminergic pathways controlling locomotion in the mouse.

Over the last decade substantial progress has been made in understanding the role of descending projections that evoke and control ongoing locomotion. Building on this work, we are exploring A11 in the posterior hypothalamus and A13 neurons in the zona incerta that contain dopaminergic neurons that project to the spinal cord and brainstem. Here we show that photostimulation of the A11 and A13 nuclei can evoke locomotor activity in mice. We present evidence that the A11 projects to the Medullary Reticular Formation (MRF), while the A13 projects to both the Mesencephalic Locomotor Region (MLR) and the MRF. In addition, both the A11 and the A13 projects fibres to the thoracolumbar spinal cord. These data suggest an expanded view of dopamine?s role in locomotion beyond the well-known nigrostriatal pathway.

Ying Zhang, Dalhousie University
The local circuits of V3 interneurons in the spinal cord

V3 interneurons (INs) in the spinal cord play important roles in generating robust and stable gaits in mammals. Previous anatomical data has shown that the majority of V3 INs are commissural however recent data collected from my lab demonstrates that V3 INs are involved in more complicated local circuits. Using the Phasor spatial light modulator (SLM) system to uncage MNI-glutamate, we are able to activate individual V3 INs, while monitoring postsynaptic reaction through whole cell patch clamp recordings. In 300um thick slices, we find, unexpectedly, that ventral V3 INs innervate ipsilateral motor neurons (MNs) and adjacent V3 INs. Some of these V3-V3 and V3-MN connections may be via electrical coupling. Using an isolated lumbar spinal cord, however, we confirm that intermediate descending V3 INs synapse to contralateral MNs. Typically a cluster of adjacent V3 INs are activated together to elicit excitatory post-synaptic potentials (EPSPs) in contralateral MNs, although inhibitory PSPs are also noted on occasion. Our current study is the first to map out the functional local circuits of spinal V3 INs and will lead us to a better understanding of locomotor mechanisms.

Alain Frigon, Université de Sherbrooke
The control of left-right coordination during locomotion by spinal circuits interacting with somatosensory feedback

The basic locomotor pattern is generated by a network of neurons within the spinal cord called a central pattern generator (CPG). It is thought that each hindlimb is controlled by its own spinal locomotor CPG and that left-right coordination is mediated by commissural interneurons. To investigate the control of left-right coordination by spinal circuits interacting with somatosensory feedback, adult cats were spinal-transected at low thoracic levels and trained to recover hindlimb locomotion. Cats were implanted with electrodes to record muscle activity (EMG, electromyography) and to stimulate peripheral nerves to evoke reflexes. After stable hindlimb locomotion recovered, cats performed tied-belt (equal left-right speeds) and split-belt (unequal left-right speeds) locomotion. The results show that cutaneous reflexes are modulated non-linearly with speed during tied-belt locomotion. Moreover, during split-belt locomotion, cutaneous reflex amplitude is smaller than what would be predicted based on belt speed. We propose that the spinal locomotor network modulates somatosensory feedback to optimize dynamic stability when changing speed and when left-right coordination is challenged.

Symposium 4:

Genetic and Optogenetic Investigation of Neural Circuit Mechanisms for Behaviours

Overview:
Chair: **MEI ZHEN**, Lunenfeld-Tanenbaum Research Institute, Sinai Health System

An ultimate goal of neuroscience is to understand the neural basis for animal behaviors. Only through a comparison of the organization and operation of neural circuits from multiple systems can fundamental principles underlying signal processing in the nervous system be extracted. In this symposium, we bring together junior and mid-career researchers who combine optogenetic and genetic approaches to study circuit mechanisms that underlie sensorimotor and cognitive behaviors in invertebrate (C. elegans and Drosophila) and vertebrate (mouse) models. Through these talks we will introduce state-of-art technology and the latest breakthroughs in dissecting the cellular mechanisms for animal behaviors in different model systems. Further, we aim to stimulate discussion on the diversity and conservation of circuit basis for animal behaviors.

Speakers:

Kenichi Okamoto, Lunenfeld-Tanenbaum Research Institute
Novel optogenetic approaches for studying spatiotemporal roles of cAMP and cGMP signalling from the synapse level to the brain cognitive function

Understanding how neuronal connections (synapses) are modulated is essential for elucidating the mechanisms of learning and memory. cAMP and cGMP are ubiquitous second messengers with a variety of essential physiological roles, and the metabolic enzymes for cAMP/cGMP pathways are excellent drug discovery targets for neuropsychiatric cognitive disorders. Pharmacological reagents and genetic manipulations have been utilized to study the mechanisms of the cAMP/cGMP signalling system. However, these approaches are limited in spatial and temporal specificity in the brain and thus the precious dynamic signalling functions remain elusive. To study the spatiotemporal dynamics and roles of cAMP/cGMP, we established optogenetic approaches to locally manipulate second messenger levels by light-sensitive enzymes that synthesize/hydrolyze cAMP/cGMP. We applied these tools to study synaptic function at hippocampal brain slices as well as cognitive performance in freely behaving mice. I will discuss our recent work which reveals rapid cAMP/cGMP functions in synaptic plasticity and memory formation.

Tomoko Oyama, McGill University
Multilevel multimodal integration enhances action selection in Drosophila

All nervous systems need to reliably transform multisensory information into appropriate motor outputs. Multisensory integration has been actively studied in the brain. Whether such integration occurs upstream of the brain, and how it is achieved at the level of cells and neural circuits, remain unknown. Here we demonstrate multisensory enhancement of rolling, an escape response naturally evoked by the sting of a parasitoid wasp in Drosophila larvae, and identify where this effect occurs within the circuitry that governs the behavior. Building on previous studies that identified larval nociceptive neurons as necessary and sufficient for rolling, we find that the frequency of rolling evoked by nociceptive neuron activation is greatly increased in the presence of vibration. We show that this integration of nociceptive and mechanosensory information occurs at a class of first-order projection interneurons as well as a pair of thoracic command neurons. EM reconstruction reveals that two distinct

pathways--one local and the other though the brain--converge onto the command neurons. Collectively, our results demonstrate multisensory integration upstream of the brain in Drosophila larvae.

Michael Hendricks, McGill University
Functional asymmetry for temporal stimulus features in C. elegans

Functional asymmetry in the brain allows for lateralized specialization in sensory, motor, and cognitive processes. In the nematode, C. elegans, neurons exhibit anatomical or functional left-right asymmetry. One of the best characterized are the ASE salt-sensing neurons. ASER is activated by salt decreases and suppressed by salt increases, while ASEL shows the opposite response. Several models have been proposed of how the ASEs might function together to compute a time derivative of salt changes (dC/dt) to drive navigation behaviour. At odds with these models is the fact that ablation of ASEL has no or minimal effects of positive or negative salt chemotaxis under a wide range of conditions. By systematically looking at ASE physiology and behavioural responses under carefully matched stimulus conditions, we found that ASEs can function separately to drive behavioural responses to the same stimulus but in different dC/dt ranges. Thus, functional lateralization in ASEs may represent specialization for environments with different stimulus distributions rather than a mechanism to enhance sensory discrimination.

Michael Gordon, University of British Columbia
Neural circuit mechanisms for integrating taste, hunger, and nutrient detection in Drosophila

Animals use chemosensory information to guide their feeding decisions. In particular, taste input is used to make simple binary decisions about whether or not to consume a food - sweet taste generally signals nutritive carbohydrates and promotes ingestion, while bitter taste serves as a warning of potential toxins and drives rejection. However, interoceptive signals also heavily weigh on these critical choices. Specific mechanisms to detect nutrients postingestively or relay satiety state provide important contextual information that informs feeding decisions. We have been investigating the mechanisms that impart hunger and satiety information to the neural circuits processing taste sensory input. Recently, we discovered a population of octopaminergic and tyraminergic neurons that directly modulate the sensitivity of bitter taste neurons in response to starvation. I will present our latest work in this area, along with new insight into the regulation of taste-independent mechanisms of sugar sensing from combining genetic manipulation of neural activity with automated, quantitative behavioral readouts.

Symposium 5:

Memory symphony: the score, the orchestra and the conductor

Chair: **LISA TOPOLNIK**, Laval University

Overview:
Every important event and every significant life episode is imprinted in our brain through memory traces. The brain?s amazing capacity to store the most essential information about our life, the so-called contextual memory, is encoded and stored through a concerted dialogue of several brain structures, including the hippocampal and rhinal cortices. It is believed that hippocampal circuitry together with the entorhinal cortex, subiculum and the medial septum take a central place in the brain cognitive map and

constitute the memory orchestra. What is the symphony played by this orchestra? Who writes the score and who is the conductor? This mini-symposium will attempt to answer these questions by highlighting several recent breakthroughs in the field of memory circuits that became possible due to ingenious combinations of multiple technologies in awake behaving rodents, including multi-site electrophysiology, optogenetics, miniaturized microscope and two-photon imaging. This symposium will bring together four outstanding scientists at different stages in their career to present novel findings on spatial and episodic memory encoding through multi-level circuit interactions.

Speakers:

Mark Brandon, McGill University
Space and time in the entorhinal-hippocampal circuit in health and Alzheimer's disease

The medial entorhinal cortex (MEC) is a high-level cortical structure that generates a neural code for location, similar to a GPS. Individual neurons in the MEC 1) create a grid of repeating spatial fields (grid cells), 2) signal the proximity to borders of the environment (boundary vector cells), or 3) respond to a particular direction in space (head direction cells). Together these cells create a rich and detailed representation of space that is important for navigation and spatial memory. I will discuss our latest work that is beginning to reveal how these cell types contribute to spatial representations found downstream in the hippocampus and how these neuronal codes undergo systematic degeneration in a mouse model of Alzheimer?s disease.

Attila Losonczy, Columbia University
Dissecting hippocampal circuits for navigation and memory

Both spatial navigation and episodic memory functions have been linked to the mammalian hippocampus, but the detailed mechanisms at cellular and circuit levels remain poorly understood. To address these questions, we use in vivo functional imaging to monitor the activity of identified microcircuits in the hippocampus of behaving mice during spatial exploration, fear learning and goal-directed learning. The talk will focus on our recent efforts aimed at dissecting functional roles of microcircuits at the dentate gyrus and at the CA1 areas of the mouse hippocampus. I will summarize how various types of dentate gyrus principal neurons ? adult-born and mature granule cells, and hilar mossy cells contribute to context encoding and discrimination. We also monitored activity in deep and superficial subpopulations of CA1 pyramidal cells, and assessed the relationship between sublayer dynamics and learning. Finally, I will present results on how goal-oriented learning is supported by disinhibitory GABAergic circuits in CA1. Together, our results demonstrate a functional division of labor among subpopulations of principal neurons during hippocampal-dependent behaviors.

Lisa Topolnik, Laval University
VIP members of the hippocampus

Inhibitory interneurons in the hippocampus provide for local and long-distance coordination of functionally connected areas. Vasoactive intestinal peptide (VIP)-expressing interneurons occupy a distinct niche in this cellular population as many of them specialize in innervating GABAergic cells and providing network disinhibition. In the CA1 hippocampus, VIP-positive cells innervate different neuronal populations with target-specific preference. We combine several complementary approaches, including the anatomical and neurochemical analyses, patch RNA sequencing, optogenetics and two-photon calcium imaging in awake head-fixed mice to explore the cellular diversity and functional role of

hippocampal VIP circuits. I will present our recent findings on molecular and transcriptomic properties of local and long range-projecting VIP neurons, their region-specific connectivity motifs and recruitment patterns during different network states in awake mice. Together, our results provide new evidence of VIP interneuron specialization in controlling cell ensembles along hippocampo-subicular axis during behavior.

Sylvain Williams, McGill University
Optogenetic manipulation and visualization of neuronal assemblies during memory formation

The medial septum (MS) provides a very large synaptic input to the hippocampus and is known to play a key role in theta rhythm generation as well as in memory formation. The MS is made-up of three-cell population using GABA, acetylcholine or glutamate. While recent data from our lab using optogenetics show that MS GABA cells play a predominant role in memory encoding and consolidation, much less is known about the glutamatergic population. We have used a combination of techniques such as optogenetic silencing and activation of glutamate MS neurons, electrophysiology and miniscope cell assembly recordings in mice performing a memory task to determine the role of these cells in memory. We provide evidence that MS glutamate neurons are causally involved in memory encoding and display specific firing in response to different behavior and time during the learning task. We therefore provide evidence for a remarkable heterogeneity of functions of the different populations of MS neurons in memory formation.

Symposium 6:

Mitochondria as a therapeutic target in Parkinson's disease

Chair: **LOUIS-ERIC TRUDEAU**, Université de Montréal

Overview:
Mitochondria are at a central position in the pathophysiology of Parkinson's disease (PD). A number of key PD-related genes encode proteins that regulate mitochondrial function, turnover and even antigen presentation. The present symposium will present recent data evaluating the possibility that elevated basal mitochondrial bioenergetics may be at the origin of the high vulnerability of key subsets of neurons in the PD brain and that targetting mitochondrial function to facilitate energy production while reducing oxydative stress may represent a viable therapeutic approach. Louis-Eric Trudeau will present work demonstrating that the particular morphological properties of vulnerable neurons in PD are at the origin of their high energy requirements and vulnerability. Joanne Nash will demonstrate that upregulation of the mitochondrial deacetylase SIRT3 can protect dopamine neurons in a rat PD model. Ruth Slack will discuss how mitochondria can be reconfigured to enhance their bioenergetics capacity. David Park will discuss the role of Pink1 in regulating the putative mitochondrial C2 /H exchanger Letm1 in regulating neuronal survival.

Speakers:

Louis-Eric Trudeau, Université de Montréal
Is increased basal bioenergetics a common property of vulnerable neuronal populations in Parkinson's disease?

Although the mechanisms underlying the loss of neurons in Parkinson's disease are not well understood, impaired mitochondrial function is suspected as playing a major role. Why dopamine neurons and a select small subset of brain nuclei are particularly vulnerable to ubiquitous cellular dysfunctions is presently one of the key unanswered questions in Parkinson's disease research. This talk will present recent data testing the intriguing hypothesis that the heightened vulnerability of these neurons is a consequence of the particular morphological characteristics of these cells, which are long range projections neurons with a highly elaborate axonal arborization and elevated bioenergetic requirements. We find that vulnerable nigral dopamine neurons differ from less vulnerable dopamine neurons such as those of the ventral tegmental area by having a higher basal rate of mitochondrial oxidative phosphorylation, a higher density of axonal mitochondria, an elevated level of basal oxidative stress and a considerably more complex axonal arborization.

Joanne Nash, University of Toronto
SIRT3 rescues dopaminergic neurons through stabilisation of mitochondrial biogenetics in a rat model of parkinsonism

Mitochondrial dysfunction is central to Parkinson's disease (PD) pathology. Sirtuin 3 (SIRT3) is a mitochondrial protein deacetylase that enhances metabolic processes to stabilise mitochondrial energetics. SIRT3-mediated modifications are associated with longevity and cytoprotection in several species including human. Since SIRT3 has multi-faceted mitochondrial health-enhancing capabilities, we hypothesized that overexpression of SIRT3 would slow PD progression. Adeno-associated virus (AAV) vectors encoding SIRT3-myc and human-A53T-mutant alpha-synuclein (hA53T-alpha-Syn) were infused into the substantia nigra (SN) of rats. When SIRT3 was delivered prior to hA53T-alpha-Syn, neurodegeneration and behavioural impairment were prevented. When SIRT3 was delivered after hA53T-alpha-Syn, when rats were already exhibiting parkinsonian motor deficits and cellular stress, SIRT3 prevented further progression of pathology and related behavioural deficits, and reversed PD-linked cellular stress. In cells, SIRT3 reduced mitochondrial bioenergetic demands, and decreases ROS production. We conclude that SIRT3 has potential as a disease-modifying agent in PD.

Ruth Slack, University of Ottawa
Mitochondrial restructuring to enhance ATP production and resistance to stress.

Sustained cellular function and viability of high-energy demanding post-mitotic cells rely on the continuous supply of ATP. The utilization of mitochondrial oxidative phosphorylation for efficient ATP generation is a function of oxygen levels. As such, oxygen deprivation, in physiological or pathological settings, has profound effects on cell metabolism and survival. We show that mitochondria can be reprogrammed to preserve efficient ATP production regardless of oxygen levels. Upregulation of key mitochondrial proteins, including Opa1, matrix-targetted Mcl1 or treatment of cells with mild acidosis triggers a reversible mitochondrial restructuring to enhance bioenergetics efficiency and reduce ROS production. We have conducted a proteomic screen to identify the key molecular targets that mediate mitochondrial reprogramming. Identifying the mechanisms by which mitochondria can be reprogrammed will open new strategies to enhance neuronal survival under stress conditions.

David Park, University of Ottawa
Letm1 as a substrate of the Parkinson's disease gene pink1.

Pink1 is a mitochondrial kinase linked with a recessive form of Parkinsons disease. However, its role in PD-related pathogenesis is not completely clear. Pink1 along with Parkin is best known to regulate mitochondrial quality control pathways to eliminate damaged mitochondria through mitophagy. In this scenario, Pink1 accumulates on the outer mitochondrial membrane in response to stress. However, Pink1 is also known to be processed and reside at the inner mitochondrial membrane. We have identified a novel target of Pink1, the Ca2+/H+ exchanger Letm1 which resides at this site. We show that Pink1 phosphorylates Letm1 and regulates exchange activity. We also provide evidence that the Pink1-Letm1 pathway is important for the degenerative pathway induced by mitochondrial stress both in vitro and in vivo.

Symposium 7:

Emerging roles of the cerebellum in shaping brain development and disease

Chair: **LU-YANG WANG**, SickKids Res Inst. & Univ. Toronto

Overview:
The cerebellum is classically associated with motor functions, but recent human and animal studies point to crucial roles in higher-order brain functions. This symposium will bring together scientists from across Canada and the States who have made outstanding contributions to the development and function of the cerebellum in health and disease, including cerebellar ataxia, autism spectrum disorders (ASD), and Fragile X Syndrome (FXS). They will discuss their exciting and largely unpublished research spanning a diverse range of approaches, from the genetics of development (Dan Goldowitz), the molecular and cellular mechanisms of synaptic transmission and plasticity (Derek Bowie & Amy Yang) and the cellular rescue of pathological motor phenotypes (Alanna Watt). This wide spectrum of research topics exemplifies the depth and breadth of basic neurobiological research and translational potentials propelled by advanced genetic and protein perturbation tools, behavioural assays, and cutting-edge in vitro and in vivo electrophysiological and imaging technologies.

Speakers:

Wang, L, SickKids Res Inst. & Univ. Toronto
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Dan Goldowitz, University of British Columbia
Exploring novel and familiar genes involved in cerebellar development

We have used microarray and now next generation technologies to examine the RNAs that are made at 24hour intervals during the embryonic development of the mouse cerebellum to create sets of data that can be mined to propose and test hypotheses concerning the developmental genetics of the cerebellum. Several short stories will be told on how these data and bioinformatics analyses, that are followed by critical validation steps, can provide novel molecular insights into the development of the normal and abnormal cerebellum. One example has been our work with the protein that is upstream in the Wnt signalling pathway, the homolog to the fly Wntless gene, Wls. We find that this gene is a novel marker for early compartmentation of the cerebellar rhombic lip, the progenitor zone of the most numerous neuron in the brain, the granule cell. When this gene is conditionally knocked out there are outcomes that are similar to the beta-catenin knockout but other phenotypes that are unique providing novel insights into the molecular pathways important for cerebellar development. Two other stories of current work will also be presented in this talk.

Amy Yang, University Of Minnesota
Molecular underpinnings of excessive inhibition in cerebellum with Autism Spectrum Disorder

Recent studies implicate the cerebellum in high-order cognitive functions beyond motor control and learning. Abnormal cerebellar activity could lead to neurodevelopmental disorders, such as autism spectrum disorders (ASD) and Fragile X Syndrome (FXS). Using fragile X mental retardation protein (FMRP) knockout mice (fmr-1-/-) as a model, we found that the firing rate of Purkinje neurons (PNs) in cerebellar slices is reduced due to excessive inhibition from GABAergic interneurons. By paired patch-clamp recordings from the basket cell (BC)-PN synapse in combination with multiphoton Ca2+ imaging as well as biochemical assays, we found that this inhibitory overtone is caused by increased excitability at the BC terminals, triggering overwhelming GABA release onto PNs. As the sole output neurons that integrate multisensory information, PNs critically gate the cerebellar output of information to regions such as the thalamus and prefrontal cortex, thereby influencing behavioral phenotypes. We conclude that the cerebellar BC-PC synapse is a new locus for genetic and drug rescue for ASD and FXS.

Derek Bowie, McGill University
Defective excitatory and inhibitory circuits of the Fragile-X brain

The talk will describe recent work from my lab linking deficits in the coupling between glutamatergic and GABAergic signaling to the neurodevelopmental disorder, Fragile-X syndrome (FXS). Although traditionally associated with motor function, emerging evidence suggests that the postnatal development of the cerebellum is also important to the onset of many features associated with autism and FXS. The talk will focus on unpublished data identifying a novel plasticity mechanism found in molecular layer inhibitory interneurons that is absent in the FXS brain. The findings point towards a new line of therapy that may counteract the deficits of FXS by targeting both glutamatergic and GABAergic synapses.

Alanna Watt, McGill University
Ameliorating motor incoordination in a mouse model of spinocerebellar ataxia

Cerebellar ataxias are a group of rare motor coordination disorders in which cerebellar degeneration is a common outcome. Recent evidence suggests, however, that cellular degeneration does not occur until

after disease onset, arguing that other pathophysiological cerebellar alterations underlie early disease stages. This talk will describe our recent studies aimed at identifying the pathophysiology of ataxia. We utilize transgenic mouse models of ataxia that recapitulate several key features of human ataxia. Using electrophysiology, imaging, and behavioural studies, we identify changes in Purkinje cell firing that accompany early disease symptoms. As the output neurons of the cerebellar microcircuit, Purkinje cells are well positioned to influence cerebellar-related motor behaviour. Chronic treatment with a drug that reverses Purkinje cell firing deficits leads to a reduction in disease symptoms in our ataxic mice. We propose that altered Purkinje cell output may represent a common change underlying motor coordination deficits in several ataxias, and thus an effective pharmacological target for disease treatment.

Symposium 8:

Stroke Recovery: From circuitry to behaviour

Chair: **DIANE LAGACE**, University of Ottawa

Overview:
In Canada, over 400,000 stroke survivors live with the after effects of stroke making it the leading cause of functional disability. In order to develop game-changing interventions to improve recovery for survivors, there is an urgent need to better understand the biology of stroke recovery from a neuronal, vascular and behavioral perspective. Dr. Lacoste, will begin the session by presenting data on the dynamic changes within the neuro-vascular unit and how this can be modified therapeutically. Dr. Murphy will then provide insights on the modification to synapses and sensorimotor circuits that occur in live mice during stroke recovery. Then, Dr. Lagace will present her data on whether neurogenesis is required or sufficient to produce improvements in stroke recovery. Finally, Dr. Corbett will close the session by describing the proportional recovery hypothesis in stroke recovery and its implications in clinical and basic research.

Speakers:

Baptiste Lacoste, University of Ottawa
Assessing Pathological Cerebrovascular Remodeling

With a poor ability to store energy, the brain is reliant on a steady supply of nutrients from the blood stream, and is thus vulnerable to vascular failures. Chronic and acute vascular abnormalities are linked to the onset and/or progression of neurological disorders including stroke. Given that no effective treatment exists for these conditions, an urgent need is to identify mechanisms involved in cerebrovascular remodeling. It is known that maintenance of vascular features (angiogenesis, blood-brain barrier, cerebral blood flow) ensures normal brain function. However, the basic principles underlying plasticity of the brain vasculature are poorly understood, and little is known about the potential benefits of modulating these mechanisms in stroke therapy. Dr. Lacoste focuses on investigating the structural, cellular and molecular basis of cerebrovascular remodeling after stroke in mice, with the goal of identifying new ways to promote post-stroke recovery. To illustrate these concepts, Dr. Lacoste will provide an example of pathological cerebrovascular remodeling in the adult mouse brain, and will present a set of approaches suitable to better characterize this phenomenon.

Tim Murphy, University of British Columbia
Automated Mesoscale Circuit and Motor Function Assessment in Mouse Models of Stroke

We describe automated forelimb and brain mesoscale imaging assessments that are geared towards stroke-recovering mice within automated homecages. We have developed a mouse training protocol and a home-cage based imaging system in which water restricted mice are trained to self-initiate headfixed imaging trials in exchange for water rewards. Up to 10 Ai94 (GCamP6s) transgenic female mice can be housed together in the automated home-cage imaging system. Mice are identified by RFID and wide-field, mesoscopic imaging of the dorsal cortex is performed to assess functional connectivity and responses to sensory stimuli. Skilled forelimb function in mice is traditionally studied through behavioural paradigms that require extensive training by investigators, and are limited by the number of trials individual animals are able to perform within supervised sessions. We developed a skilled lever positioning task that mice can perform within their home cage. The Raspberry Pi minimizes cost and maximizes the potential to scale up the automated home-cage imaging to many vivarium hosted, remote controlled cages to assess aspects of stroke recovery.

Diane Lagace, University of Ottawa
Neurogenesis and Stroke Recovery

Adult neurogenesis is hypothesized to promote stroke recovery. Post-mortem and preclinical studies demonstrate that stroke increases the number of progenitor cells (PCs) and these PCs ectopically migrate to surround the infarct in the adult brain. There are also many positive correlations between increased neurogenesis and improved recovery. Over the last decade extensive efforts have been aimed at developing and translating the knowledge about neurogenesis into new stroke therapies. One of the limitations to this translation is that it remains unclear whether neurogenesis per se causally supports recovery and whether the adult-generated cells can integrate into circuitry. Dr. Lagace will show complementary loss- and gain-of-function rat and mouse models that can specifically modulate neurogenesis and the resulting effects on behavioural recovery and cognitive function. Additional electrophysiological studies will further highlight the presence of adult-generated immature neurons in the peri-infarct cortex that can fire action potentials and receive GABAergic synaptic input. Together these findings functionally dissect the role of adult neurogenesis during stroke recovery.

Dale Corbett, University of Ottawa
Stroke Recovery: Does Rehabilitation Matter?

Human upper limb recovery is accurately predicted by initial post-stroke impairment alone. This "proportional recovery rule", implies that functional improvements are mainly due to processes of spontaneous biological recovery and not the result of rehabilitation. Here we establish that the proportional recovery rule also exists in rat models of stroke with one important caveat. Rehabilitation is necessary to reliably predict recovery as infarct volume and initial impairment increase; more intensive rehabilitation is required to engage recovery. Notably, recovery is possible regardless of stroke severity if a threshold intensity of rehabilitation is achieved. In this model, we can accurately prescribe the specific dose of daily rehabilitation required to achieve significant motor recovery using the biomarkers of initial post-stroke impairment and infarct volume. This algorithm offers a personalized medicine approach to stroke rehabilitation, wherein imaging and functional biomarkers can be used to develop an optimized rehabilitation paradigm for individual patients, particularly those with severe impairments who presently are often not the recipients of effective rehabilitation.

Symposium 9

Epigenetics, DNA Methylation, and Mental Health

Chair: **MOJGAN RASTEGAR**, University of Manitoba

Overview:
Epigenetics control gene expression through mechanisms that are not directly reflected by the underlying DNA sequences. These include different types of DNA methylation, histone post-translational modifications, and chromatin structure, among others. Recent discoveries have highlighted the importance of epigenetics and neuroepigenetics in the brain development, function, neuroscience, and mental disability. This proposed parallel symposium is an exciting gathering of four neuroepigenetic experts in Canada whose research is directly linked to neuroscience and mental health. Each speaker will present a topic related to epigenetics/DNA methylation and the impact in neuroscience and mental health. Juan Ausio (U. Victoria): Functional aspects of native and mutant MeCP2 biology Nathalie Berube (Western University): Chromatin organization in the developing brain Patrick McGowan (U. Toronto): The impact of adversity on the DNA methylome Mojgan Rastegar (U. Manitoba): A multi-level epigenetic deregulation in the brain of Rett Syndrome patients This symposium will cover exciting recent discoveries in epigenetics that impact in neuroscience and mental health.

Speakers:

Mojgan Rastegar, University of Manitoba
A multi-level epigenetic deregulation in the brain of Rett Syndrome patients

Epigenetics control gene expression and brain development through mechanisms that are not dictated by genomic DNA. Recent discoveries have underscored the importance of epigenetics and DNA methylation in the brain development, function, neuroscience, and mental health. Rett Syndrome (RTT) is a severe neurodevelopmental disease caused by loss-of-function mutations in the main DNA methyl-binding protein of the brain, called MeCP2. RTT has no cure, and the disease mechanism is not fully understood. While MECP2 gene was discovered almost quarter-century ago, we are still far from understanding the functional properties of MeCP2 in the brain. In this presentation, I will discuss the complexity of RTT pathobiology, contribution of MeCP2 protein variants (isoforms), and a multi-level epigenetic deregulation in the human RTT brain. Moreover, I will present our recent results and discuss how molecular deficiencies at the cellular levels cause compromised brain function in RTT, and other MeCP2-associated brain disorders such as autism.

Nathalie Berube, Western University
Chromatin organization in the developing brain

CCCTC-binding protein (CTCF) is a ubiquitously expressed chromatin organizer and the only insulator protein in vertebrates. CTCF promotes DNA looping by simultaneously binding to DNA and other proteins, including the cohesin complex. CTCF-mediated DNA loops are required for promoter-enhancer interactions and the insulator function of CTCF. Emerging evidence suggest that CTCF is required for normal functioning of the central nervous system. De novo mutations in one copy of the human CTCF

gene were recently identified in four patients with microcephaly, intellectual disability, and short stature. Moreover, polymorphisms in and around the CTCF gene were found to be linked to schizophrenia. In this presentation, I will discuss the effects of conditional CTCF deletion in the developing mouse brain and how they might relate to the associated neurological disorders.

Patrick McGowan, University of Toronto
The impact of adversity on the DNA methylome

There is accumulating evidence that the DNA methylome is sensitive to environmental stressors. These include classic forms of adversity such as psychosocial stress but also dietary stressors and environmental toxins. For example, we have found that exposure to high fat diet in development leads to marked effects on physiological and behavioural responses to stress that persist into adulthood. We have been performing studies to integrate functional and epigenome-wide DNA methylation data to investigate the extent to which these exposures target stress-related phenotypes. We will discuss challenges associated with genome-wide data integration in rodent models and humans in terms of the extent to which these hypothesis-generating approaches can be used to predict biomarkers of stress-related exposures and examine the etiology of stress-related phenotypes.

James Davie, University of Manitoba
DNA Methylation and FASD

Prenatal alcohol exposure resulting in Fetal Alcohol Spectrum Disorder (FASD) is the most common cause of neurodevelopmental impairments in the western world, with an estimated prevalence of 2-5%. DNA methylation associated with alcohol exposure could be a potential mechanism through which expression of genes involved in neurogenesis are altered during fetal stages. A recent report on the DNA methylation patterns of human FASD buccal epithelial cells presented supporting evidence for altered DNA methylation patterns in FASD samples. Results from our study identifying differentially methylated regions in rat fetal brains exposed to alcohol will be presented.

Symposium 10:

New Insights into Reconsolidation

Chair: **KARIM NADER**, McGill University

Overview:
An Abrupt Transformation of Phobic Behavior After a Post-Retrieval Amnesic Agent. We tested whether disrupting reconsolidation would also diminish fear in individuals who had developed a persistent spider fear outside the laboratory. Spider-fearful participants received a single dose of 40 mg of the noradrenergic β-blocker propranolol (n = 15), double-blind and placebo-controlled (n = 15), after a short 2-min exposure to a tarantula. To test whether memory reactivation was necessary to observe a fear-reducing effect, one additional group of spider-fearful participants (n = 15) received a single dose of 40 mg propranolol without memory reactivation. Disrupting reconsolidation of fear memory transformed avoidance behavior into approach behavior in a virtual binary fashion-an effect that persisted at least 1 year after treatment. Interestingly the β-adrenergic drug did initially not affect the self-declared fear of spiders but instead these reports followed the instant behavioral transformation several months later.

Our findings are in sharp contrast with the currently pharmacological and cognitive behavioral treatments for anxiety and related disorders.

Speakers:

Karim Nader, McGill University
Recovery from Amnesia is Fool's Gold; specific impairments in consolidation, reconsolidation and long-term memory maintenance lead to memory erasure.

Recently, several studies have demonstrated that performance reduction (amnesia) induced by blockade of consolidation, reconsolidation, or long-term memory (LTM) maintenance can lead to amnesia reversal after "reminder" presentations. These results are taken as evidence that the initial amnesia was due to a retrieval impairment that the reminders overcame. A problematic that this purely behavioral approach only measured levels of performance. However since the early seventies, interpretations have been formulated which are consistent with the performance impairment being caused by a storage impairment. The reminders induce performance enhancements by strengthening the residual memory, which also predict amnesia reversal. The definitive solution to address this issue is to examine what happens to the brain correlates of LTM (BC-LTM). If a specific impairment in consolidation, reconsolidation, or LTM is due to a storage impairment, then the BC-LTM should be close to untrained animals. If the amnesia is due to a retrieval impairment of an existing memory in the brain, the levels of BC-LTM should remain unchanged. No study to date has been consistent with the retrieval impair

BK Kaang, Seoul National University
Multiple repressive mechanisms in the hippocampus during memory formation.

Memory stabilization after learning requires translational and transcriptional regulations in the brain, yet the temporal molecular changes that occur after learning have not been explored at the genomic scale. We used ribosome profiling and RNA sequencing to quantify the translational status and transcript levels in the mouse hippocampus after contextual fear conditioning. We revealed three types of repressive regulations: translational suppression of ribosomal protein-coding genes in the hippocampus, learning-induced early translational repression of specific genes, and late persistent suppression of a subset of genes via inhibition of estrogen receptor 1 (ESR1/ERα) signaling. In behavioral analyses, overexpressing Nrsn1, one of the newly identified genes undergoing rapid translational repression, or activating ESR1 in the hippocampus impaired memory formation. Collectively, this study unveils the yet-unappreciated importance of gene repression mechanisms for memory formation.

Martin Cammarota, Federal University of Rio Grande do Norte
How to break the constraints on reconsolidation

The predominant view about memory formation states that a consolidation process stabilizes newly acquired traces until they are safely stored in the brain. However, during the last ten years evidence has accumulated to indicate that, upon retrieval, consolidated memories are rendered again vulnerable to the action of metabolic blockers, notably protein synthesis inhibitors. This has led to the hypothesis that memories are reconsolidated at the time of retrieval, and that this requires protein synthesis in different brain regions. Here we will address the consolidation-reconsolidation debate and discuss some controversial issues about the reconsolidation hypothesis, in particular the biological role of this process.

Merel Kindt, University of Amsterdam
An Abrupt Transformation of Phobic Behavior After a Post-Retrieval Amnesic Agent

BACKGROUND: Although disrupting the process of memory reconsolidation has a great potential for clinical practice, the fear-amnesic effects are typically demonstrated through Pavlovian conditioning. Given that older and stronger memories are generally more resistant to change, we tested whether disrupting reconsolidation would also diminish fear in individuals who had developed a persistent spider fear outside the laboratory. METHODS: Spider-fearful participants received a single dose of 40 mg of the noradrenergic β-blocker propranolol (n = 15), double-blind and placebo-controlled (n = 15), after a short 2-min exposure to a tarantula. To test whether memory reactivation was necessary to observe a fear-reducing effect, one additional group of spider-fearful participants (n = 15) received a single dose of 40 mg propranolol without memory reactivation. RESULTS: Disrupting reconsolidation of fear memory transformed avoidance behavior into approach behavior in a virtual binary fashion-an effect that persisted at least 1 year after treatment. Interestingly the β-adrenergic drug did initially not affect the self-declared fear of spiders but instead these reports followed the instant behav

Symposium 11:

Estrogen's effect on cognition and the brain: A translational perspective

Chair: **GILLIAN EINSTEIN**, University of Toronto

Overview:
Estrogens Effects on Cognition and the Brain: A translational perspective Hormones play a fundamental role in shaping brain function. A large body of evidence across species indicates that 17-beta-estradiol (E2) modulates cognition and brain function in key regions involved in mnemomic processing, e.g. hippocampus, perirhinal, and prefrontal cortex. Importantly, E2 affects these regions across age and reproductive stage. This symposium will take a translational approach to delineating E2's role in learning and memory. Dr. Galea will present her work on estrogens, cognition and neurogenesis in rat hippocampus. Dr. Gervais will present her work on recognition memory in female rats and women with prophylactic bilateral oophorectomy prior to natural menopause. Dr. Morrison will present findings from his studies on prefrontal dependent cognition in female macaques with OVX prior to natural menopause. Dr. Hampson will discuss her research showing E2's effects on frontal cortical memory in peri- and menopausal women. Dr. Gillian Einstein will co-chair with Dr. Annie Duchesne.

Speakers:

Gillian Einstein, University of Toronto
The effect of estrogen depletion on verbal memory in young women

Estrogens have an effect on both female and male brains profoundly affecting growth of neuronal synapses and processes in the hippocampus with some evidence suggesting that the effects are different for each sex. For women, estrogens have been implicated in neurological conditions and its withdrawal has long been thought to be a risk factor for Alzheimer's disease. In this talk I will discuss the importance of considering hormones in both basic and clinical research as well as the effects of estrogen

depletion on verbal memory in young women. Research on women with ovarian removal prior to natural menopause in order to alleviate the risk of inherited cancers reveals decreased verbal memory and fluency, underscoring the importance of ovarian steroids for younger women's brain health.

Nicole Gervais, University of Toronto
Impact of ovarian hormones on recognition memory and perirhinal cortex in rats and humans

Loss of ovarian function associated with natural menopause is related to cognitive impairments and increased risk of mild cognitive impairment and Alzheimer?s disease (AD) later in life. This risk is further increased following surgical removal of the ovaries prior to natural menopause (OPNM). Animal models have demonstrated protective effects of estradiol (E2) on several cognitive domains, including visual recognition memory. This ability is dependent on the perirhinal cortex (PRh), a structure that is damaged in the early stages of MCI and AD. A review of three studies examining the impact of local actions of E2 in the PRh of ovariectomized rats will be discussed. Recent data from women that had prophylactic OPNM will also be presented, including results from the Remember/Know paradigm, and its relation to cortical thickness in the PRh. The relevance of these data with respect to potential early markers of onset of MCI/AD will be discussed, as well as directions for future research.

Agnès Lacreuse, University of Massachusetts
Neurocognitive effects of estrogens in female non-human primates across the adult lifespan

Mounting evidence indicates that estrogens affect many aspects of hippocampal and prefrontal function. In addition, estrogens may also influence cognitive function indirectly, via the modulation of other systems that impact cognition, such as sleep. This presentation will focus on the effects of ovarian hormone manipulations on cognitive performance in rhesus monkeys and marmosets in the context of aging and surgical menopause. Additional findings on the effects of estradiol on sleep and their potential role in modulating cognition will be discussed.

Elizabeth Hampson, Western University
Estrogen's Effects on Frontocortical Memory in Peri- and Postmenopausal Women

The medial temporal lobe is often considered a primary site for estrogen action in the adult female brain and a probable substrate for the effects of surgical and natural menopause on memory function. A smaller body of literature, beginning in the late 1990s, points to the potential importance of estrogen in the prefrontal cortex. Convergent evidence for this point of view has come from cellular and molecular studies of nonhuman primates, and from cognitive and imaging studies in humans. This presentation will review some of the human evidence suggesting that estrogens are important regulators of function in the prefrontal cortex, including work from our own laboratory on working memory. Recent evidence suggests that estradiol is an important influence on working memory function, also, in young women of reproductive age and that its role may extend beyond working memory to other functions dependent on the dorsolateral cortex.

Symposium 12:

Mechanisms of Neuronal Migration and Regeneration

Chair: **CLAIRE BENARD**, UQAM / UMass Medical School

Overview:
Proper wiring of neuronal circuits relies on the guidance of migrating neurons and processes during development, and after their initial assembly, the integrity of neuronal circuits needs to persist throughout life. Studies using the complementary model organisms Caenorhabditis elegans and mice, have been key in elucidating conserved pathways regulating neuronal development, maintenance and regeneration. In this Parallel Symposium, four complementary talks will feature key advances in understanding of the regulation of neuronal migrations, the maintenance of neuronal architecture and axon regeneration in the nematode and mice. Dr. Pilon will report on migrations of the enteric nervous system in mice, Dr. Bénard will discuss the role of proteoglycans in regulating axon guidance and maintenance in C. elegans, Dr. Kennedy will talk on the role of glycosaminoglycans and netrin in guidance in mice, and Dr. Byrne will present her research on axon regeneration in C. elegans.

Speakers:

Nicolas Pilon, UQAM
Fam172a is critically required for neural crest cell migration and proliferation

In vertebrate embryos, the multipotent neural crest cells (NCCs) migrate from the dorsal neural tube in order to generate a wide array of cell types such as peripheral neurons and glia, melanocytes, and craniofacial chondrocytes. To identify new genes important for NCCs, we performed an insertional mutagenesis screen in the mouse. In one of the lines, named Toupee, we observed a complex phenotype reminiscent of human CHARGE syndrome. The Toupee insertion site disrupts a poorly characterized - but highly conserved - gene called Fam172a. This mutation has a major impact on the NCC transcriptome, notably resulting in defective proliferation and migration. The Fam172a protein possesses serine hydrolase activity and is predominantly located in the nucleus where it appears to bridge chromatin-associated proteins and splicing factors. One of the Fam172a-binding proteins is the chromatin remodeler Chd7 - for which loss-of-function is currently the only known cause of CHARGE syndrome - and analysis of splicing in Toupee and Chd7 mutant embryos suggests that uncoupling of transcription with alternative splicing might be a common pathogenic mechanism for all cases of CHARGE syndrome.

Claire Benard, UQAM
Extracellular modulators of axonal guidance and long-term neuronal protection

Nervous system function relies on the assembly of neural circuits during development and their long-term protection. Whereas key molecules that guide migrating neurons have been identified, how the cellular responses to these cues are orchestrated during development is unclear. Similarly, how the neural circuits established during embryogenesis are maintained during subsequent development remains largely unexplored. Using C. elegans, we uncovered roles for heparan sulfate proteoglycans (HSPGs) in guiding migrations, including the requirement for the coordinated HSPG synthesis in both the migrating neuron and its substrate. Also, we found that the HSPG LON-2/glypican acts as an extracellular modulator of UNC-40/DCC to fine-tune axonal responses to UNC-6/netrin signals during migration. In addition, through genetic screens we have identified neuronal maintenance molecules (e.g. SAX-7/L1CAM and NEMA-1), which function post-embryonically to protect neuronal architecture in the face of growth and movement. Our findings provide insights into general principles underlying HSPG function in neural development as well as into conserved mechanisms that maintain neuronal architecture.

Timothy Kennedy, MNI/McGill
Netrin-1 and GAG Function in CNS Perineuronal Nets

Perineuronal nets (PNNs) are a specialized extracellular matrix that develops relatively late during CNS maturation. PNNs ultimately envelop many neuronal cell bodies, dendrites, and synapses in a dense web of glycosaminoglycans (GAGs), including chondroitin sulfate proteoglycans (CSPGs), that exerts a potent influence on synaptic plasticity and regeneration. Netrin-1 is a secreted axon guidance cue that can inhibit or promote axon growth during neural development. We have found that netrin-1 is enriched at synapses and regulates synaptic plasticity in the mature mammalian CNS. Netrin-1 binds chondroitin sulfate and heparan sulfate sugars, and our findings reveal binding to CNS CSPGs and the related family of heparin sulfate proteoglycans (HSPGs). CSPGs and HSPGs are important components of CNS extracellular matrix at all stages of development and maturation, and like netrin-1, CSPGs and HSPGs can promote or inhibit axon growth. Our ongoing studies address the functional significance of interactions between netrin-1 and CSPG and HSPG proteoglycans and their relationship to PNNs in vivo.

Alexandra Byrne, UMass Medical School
Poly(ADP-Ribosylation) Regulates Axon Regeneration

Few of the intrinsic mechanisms that regulate axon regeneration after injury are known. To identify genes that regulate axon regeneration, we compared gene expression profiles of FACS-sorted C. elegans GABA motor neurons with high regenerative capacity to wild type GABA motor neurons. Both poly(ADP-ribose) glycohydrolases (PARGs), parg-1 and parg-2, were upregulated in neurons with high regenerative capacity. To test the hypothesis that PARG activity promotes axon regeneration, we performed laser axotomy in parg-1 and parg-2 loss-of-function mutants and found regeneration is impaired in both mutants. Therefore, PARGs promote axon regeneration. Since PARGs degrade poly(ADP-ribose) synthesized by poly(ADP-ribose) polymerases (PARPs), we hypothesized PARGs and PARPS have opposite roles in axon regeneration. Indeed, we found loss of parp-1 and parp-2 gene function increased axon regeneration and chemical PARP inhibition after injury improved functional regeneration. Together, our findings identify PARGs and PARPs as novel regulators of axon regeneration.

Poster Abstracts

Monday, May 29, 2017

A - Development

1-A -1 Migrating interneurons secrete fractalkine to promote oligodendrocyte formation in the developing mammalian brain

Anastassia Voronova[1], Scott Yuzwa[1], Beatrix Wang[1], Siraj Zahr[1], David Kaplan[1], Freda Miller[1]
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During development, newborn interneurons migrate throughout the embryonic brain. Here, we provide evidence that these interneurons act in a paracrine fashion to regulate developmental oligodendrocyte formation. Specifically, we show that medial ganglionic eminence (MGE) interneurons secrete factors that promote genesis of oligodendrocytes from glially-biased cortical precursors in culture. Moreover, when MGE interneurons were genetically ablated in vivo prior to their migration, this caused a deficit in cortical oligodendrogenesis without affecting the number of microglial cells. Modelling of the interneuron-precursor paracrine interaction using transcriptome data identified the cytokine fractalkine as responsible for the pro-oligodendrocyte effect in culture. We show that fractalkine is expressed in migrating MGE interneurons and that MGE-interneuron ablated embryos display reduced levels of fractalkine-expressing cells in the cortical SVZ area, where newborn oligodendrocyte progenitor cells (OPCs) reside. We further demonstrate that OPCs express fractalkine receptor CX3CR1 in vivo and that the knockdown of CX3CR1 in embryonic cortical precursors, or constitutive knockout of CX3CR1 caused decreased numbers of OPCs and oligodendrocytes in the postnatal cortex. Thus, in addition to their role in regulating neuronal excitability, interneurons act in a paracrine fashion, at least in part through fractalkine signalling, to promote the developmental genesis of oligodendrocytes.

1-A -3 Role of glycinergic activity in neurogenesis during embryonic development.

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[1]crCHUM

Introduction: Glycine and GABA induce fast synaptic inhibition in mature neurons. In contrast, these transmitters are excitatory and generate the first electrical signal in immature neurons and their progenitors. This switch in glycine signals is due to developmental alteration of the chloride gradient but its roles are still unclear. The aim of this project is to understand the role of this switch in regulating progenitor differentiation. Methods: We used transgenic zebrafish lines expressing GFP in neural progenitors (GFAP or Nestin). We disturbed glycine signals by morpholino knockdowns and then analyzed the GFP signal. In parallel, we analyzed the nestin and gfap populations by in situ hybridization. Apoptosis was assayed by immunofluorescence to detect activated caspase 3 or in vivo by acridine orange staining. We also analyzed the cell autonomous action of glycine receptors by mosaic analysis. Donor embryos were labeled with a membrane and nucleus marker in both conditions, control and morphant. Then, cells from donor embryos were transplanted into the wt host embryo and visualized by confocal microscopy. Results: We found that perturbation of glycine activity in vivo induced a selective loss of the nestin progenitor population, but not the GFAP population. Moreover, we observed increased apoptosis at early stages. Mosaic analysis revealed that many progenitors died before

maturation. Conclusion: These findings reveal that glycinergic activity plays an important cell autonomous role in progenitor survival and differentiation, particularly in the nestin population.

1-A -4 Intersectional genetic labelling of ascending spinal and sensory neuron projections

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Sensory neuron signals enter the dorsal horn of the spinal cord and are processed by local circuits before being relayed to the brain via spinal projection neurons (SPNs). A direct connection between sensory neurons and dorsal column nuclei also exists. Functional dissection of such ascending pathways has been hampered by the lack of their molecular characterisation. To resolve this shortcoming, we are using transgenic mice in which the Cre recombinase is under the control of Math1 and Isl1 promoters, to uncover the projection targets of molecularly-defined SPNs. Adult nervous system Math1:Cre and Isl1:Cre expression was mapped using a Cre reporter. These mice were given two treatments: 1) Retrograde tracer dye injection into brain areas containing Cre reporter+ axons and 2) an injection of formalin in the right forepaw to label spinal nociceptive neurons. An analysis of cFos, Cre Reporter and retrograde tracer in spinal neurons led us to conclude that Math1:Cre and Isl1:Cre label a large population of deep dorsal horn neurons, but label few SPNs, and are not significantly involved in nociception. To determine whether spinal Math1:Cre and Isl1:Cre neurons have any brain projections, we have generated mice containing both Cre and Cdx2:FlpO (expressed only in the spinal cord and dorsal root ganglia) and a Cre/FlpO intersectional reporter. As Math1:Cre and Isl1:Cre are expressed extensively within the brain, this strategy allows us to exclusively study reporter+ projections of neurons in the spinal cord and dorsal root ganglia.

1-A -5 Spatial regulation synapse formation by Plexin/Rap signaling in C. elegans

Kelly Xi Chen[1], Kota Mizumoto[1]
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Fineness of the neurocircuit is ultimately determined by the resolution of single neuron and synapse. Due to the complexity of the nervous system, however, it is not easy to study the molecular mechanisms of fine neuronal map formation in the mammalian nervous system. Using C. elegans, we reported that one of the axon guidance molecules, Semaphorin (Sema) and its receptor, Plexin, play critical role in establishing fine synapse map formation by locally restricting synapse formation to the specific sub-axonal region. In contrast to the pivotal role of Sema/Plexin signaling in axon guidance in vertebrates and fly, mutants of sema and plexin did not show obvious axon guidance defects. The specific phenotype of sema and plexin in synapse patterning provides us a unique experimental platform to examine their roles in synapse map formation. To understand how Sema/Plexin signaling regulates synapse patterning, we looked for the intracellular signaling components that link Plexin and synapses. Plexin was recently shown to act as a RapGAP (Rap GTPase activating protein), which inactivates Rap small GTPase. Consistently, we observed that gain-of function mutant of Rap-2, which is an ortholog of mammalian Rap2, mimicked the synaptic phenotype of plexin mutants. Surprisingly, however, loss-of function of Rap-2 also showed the same synaptic defect as its gain-of-function mutants, suggesting that the cycling of Rap-2 activity is spatially regulated by Plexin. We will discuss about the spatial regulation of Rap-2 activity by Plexin and their roles in synapse formation.

1-A -6 A BioID experiment to identify proximal interactors of EphB2

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Ephrin-B:EphB signalling plays important roles in many tissues during development, including the guidance of spinal motor axons. However, the cascade activated downstream of their binding remains only modestly understood. To further characterise this molecular system, we performed BioID followed by mass spectrometry analysis to identify proximal interacting partners of EphB2. We used a stable HEK293 cell line expressing an inducible EphB2-BirA*-FLAG construct, and exposed cells to ephrin-B2 or control ligands. The experiment was performed twice, with two replicates in each condition, allowing for powerful statistical analysis. Our results identified several hundred proteins either preferentially found in the ephrin-B2-stimulated condition ("recruited" by stimulation) or in the control conditions ("excluded" by stimulation). Many others were present in all conditions with an unchanging score. Predictably, some of the top hits are known EphB-binding partners like Abl2, Shp2, Afadin, and Nck. Importantly, these known interactors all had higher scores in the stimulated condition, suggesting they are recruited to EphB2 upon ephrin-B2 binding. Moreover, our stringent statistical analysis also identified dozens of proteins with no previously reported link to EphB signalling. These include tyrosine phosphatases, membrane trafficking molecules, and proteins associated with the trans-Golgi network. We are currently investigating the role of these molecules in ephrin-B:EphB signalling in the context of spinal motor axon guidance, both in vitro and in vivo.

1-A -7 Depressive Symptoms and The Evolution of Executive Functions in The Course of Adolescence: A Longitudinal Study

Mohammad Hassan AFZALI[1], Maeve O'Leary Barrett[1], Lea Noirhomme[1], Sira Maiga[1], Sherry Stewart[2], Robert Pihl[3], Jean Seguin[1], Benoit Masse[1], Patricia Conrod[1]
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Executive function (EF) impairments are widely recognized as an important aspect of depression. Neuropsychological studies indicate that the prefrontal cortex (PFC) is of critical importance for EFs. During the adolescence the PFC is undergoing a protracted course of neurodevelopment related to the gradual development of EFs. Therefore, the study of the association between depression and EFs among adolescents requires developmentally sensitive examination of executive functions through longitudinal data. The aim of current study is to examine the concurrent and lagged effects of depressive symptoms on the initial level and the evolution of four EFs (i.e., working memory, delayed memory, reasoning, and inhibition) in a multilevel framework. As a part of Coventure project depressive symptoms and the aforementioned EFs of 3825 Canadian adolescents were assessed in the course of four years. Results indicate that higher number of current and past year depressive symptoms is associated with worse performance in the delayed memory task. Likewise, higher number of past year depressive symptoms is associated with worse performance in the working memory task. These negative effects are stronger through early adolescence. The reported findings suggest that the presence of depressive symptoms affect the development of EFs and underlines the necessity of the early intervention programs among young adolescents to decrease the subsequent harms. Moreover, the effect of early onset depression on the underlying neural substrates deserves further investigation among adolescents.

1-A -8 Bound and GAGed: Molecular Mechanisms Localizing Netrin-1 in Neural ECM

Stephanie Harris[1], Heleen van't-Spijker[2], Celina Cheung[1], K. Adam Baker[1], Simon Moore[1], James Fawcett[2], Timothy Kennedy[1]
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Axons often travel long distances to reach their targets during development. Netrin-1 is a bi-functional axon guidance protein that can attract or repel extending axons and is crucial for proper spinal cord

development. Commissural neurons, born in the dorsal embryonic spinal cord, extend axons to the ventral midline where the concentration of netrin-1 is high. The netrin-1 receptor Deleted in colorectal cancer (DCC) is expressed by commissural neurons and required for the chemoattractant response to netrin-1. Netrin-1 protein is comprised of three major domains; the laminin related domains VI and V, and an NTR-like C domain. Domains VI and V contain sequences that bind DCC while the C domain has no known function. We are investigating the possibility that netrin-1 may be localized and anchored in the extracellular matrix (ECM) through specific interactions of the C-domain with ECM Glycosaminoglycans (GAGs). GAGs are expressed in both developing and adult CNS, and composed of a core protein decorated with multiple unbranched sugar side chains on both ends of the amino acid chain. We are particularly interested in the Heperan Sulfate Proteoglycan (HSPG) and Chondroitin Sulfate Proteoglycan (CSPG) subfamilies. Our findings indicate that netrin-1 binds HSPGs and CSPGs isolated from adult rat brain, and that HSPGs increase axon outgrowth in response to netrin-1. We are currently investigating possible interactions between netrin-1 and GAG protein rich perineuronal nets (PNN) that regulate synapse function in the adult brain.

1-A -9 Do Cannabinoids participate to synaptogenesis ?

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Through their two main receptors CB1R and CB2R, cannabinoids (CBs) participate to axon guidance (Argaw et al., 2011; Duff et al., 2013). Because several molecules that direct neurite extension also regulate synapse formation, we investigated a novel function for CBs and their receptors regulating synaptogenesis. The present study was performed on mouse cortical neurons in vitro, a simple model convenient to study a complex phenomenon such as synaptogenesis. CB1R and CB2R activity was modulated either with pharmacological agents or genetic tools. Cellular and molecular experiments were confirmed using functional assays. A pharmacological approach combined with immunocytochemical analysis showed an increase of synaptic precursors and contacts on neurons treated with inverse agonists of CB1R or CB2R, and conversely, the agonists induced a decrease. Then, the presynaptic function has been addressed using a fluorescent membrane probe (FM1-43). Our results suggested that the anatomical increase of synaptic contacts could be related with an enhancement of the presynaptic function. To address whether CB1R and CB2R modulate the number of functional synapses, we recorded excitatory postsynaptic currents using patch clamp. Identification of mechanisms that underlie synapse formation remains a fundamental question in neuroscience and will help in developing cures aiming at the treatment of neurodegenerative diseases. Otherwise, the detrimental effects of cannabis on the developing nervous system are not fully understood, and the present work could provide potential mechanisms of action

1-A -10 Role of Fragment C and Msx3 in the spinal development of zebrafish.

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Radial glial cells (RGCs) are progenitor cells that generate neurons and glia during embryonic and larval neural development. In fish, RGCs continue to act as neural progenitor cells into adulthood. The Msx3 gene is part of the evolutionarily conserved Msx class of genes encoding transcription factors, some of which are involved in the dorsal development of mammalian spinal cords. Our preliminary data suggested that Msx3 is expressed in cells of the zebrafish dorsal spinal cord so we sought to determine if Msx3 is involved in its development. To test for coexpression of GFP and RGC markers, immunohistochemistry was conducted on a transgenic zebrafish strain Tg(fragCmsx3+βG:eGFP) where

GFP expression is under the control of Fragment C, an enhancer of the Msx3 gene. 2-5dpf transgenic zebrafish larvae were sectioned and stained with antibodies against markers for mature neurons (HuC), RGCs (GFAP), neural progenitors (Sox2), and astrocytes (BLBP). Our data showed GFP expression strictly in the dorsal spinal cord while expression of markers for mature neurons, RGCs, neural progenitors and astrocytes was widespread in the spinal cord. Despite observing no colabelling between GFP and HuC, we found co-expression of GFP and markers for RGCs, neural progenitors, and astrocytes and thus shown that the Msx3 gene is expressed in RGCs in the dorsal spinal cord of zebrafish. Considering that RGCs generate both glia and neurons early in development, our findings suggest that Msx3 contributes to the development of the zebrafish dorsal spinal cord through its expression in RGCs.

1-A -11 Activation of quiescent adult neural stem cells via targeted stimulation of EGFR signaling

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Neural stem cell (NSC) activity is altered in many biological contexts such as neurodegenerative diseases, causing defects in cognitive functions and brain repair capacity. A deeper understanding of the mechanisms underlying NSC activation therefore has important implications for NSC recruitment under pathological conditions. Here, we explore the involvement of epidermal growth factor receptor (EGFR)-induced signaling in NSC activation. Expression of EGFR is dynamically regulated in the NSC lineage, as it is absent on quiescent NSCs (qNSCs) but is expressed by the proliferatively active NSC (aNSCs) population, and EGF is sufficient to stimulate proliferation of aNSCs and their downstream progenitors in vitro. Loss-of-function analysis of individual EGFR-induced pathways using specific pathway inhibitors in NSC cultures revealed differential requirements for EGFR-induced mTOR, AKT and ERK pathways for neural precursor survival, proliferation and/or differentiation. We then developed an electroporation approach to specifically activate EGFR signaling pathways in ventricle-contacting qNSCs. Examination of early time-points following electroporation shows evidence that the genetically targeted qNSCs begin progressing down the activation pathway. Fate-mapping (in progress) will reveal whether direct genetic stimulation of EGFR signaling in the qNSC pool is sufficient to promote NSC activation and neurogenesis.

1-A -12 1,2-dibromo-4-(1,2-dibromoethyl)-cyclohexane (TBECH) alters dendritic development of cultured Purkinje neurons.

Rebecca van Ginkel[1], Brittany Stojak[1], Tammy Ivanco[1], Gregg Tomy[1], Mark Fry [1]
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Brominated flame-retardants (BFRs) are environmentally pervasive and persistent synthetic chemicals that have been shown to disrupt neuroendocrine signalling and neural development. These observations have led to restrictions on the use of specific compounds and as a result, alternative BFRs, such as 1,2-dibromo-4-(1,2-dibromoethyl)-cyclohexane (TBECH), have come into widespread use. TBECH has been reported to lack the toxicity of other classes of BFRs, however its safety is still questioned. The structural similarities of TBECH to other BFRs suggest TBECH may interrupt thyroid hormone signalling and neural development. This pilot study aimed to evaluate the effects of developmental TBECH exposure on dendritic morphology in Purkinje neurons. Primary cultures of neonatal rat cerebella were maintained under control conditions or in the presence of 10 μM TBECH for 21 days, at which time neurons were fixed and immunostained for calbindin D28K. Neuronal morphology was analyzed with Sholl analyses. While critical radius, number of primary branches, and maximum radius were unaffected, ramification indices differed significantly ($p=0.00755$) between control and treated neurons. TBECH-exposed neurons show higher ramification indices (mean of 7.207 versus 5.314 for control), indicative of increased branching per primary dendrite. These data indicate that exposure to TBECH may compromise the

ability of Purkinje neurons to correctly process synaptic information, which could be detrimental to cerebellar functions including motor control, coordination, and cognition.

1-A -13 Shunting GABAA Transmission Regultates Glutamatergic Synapse Formation in the Developing Hippocampus

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GABA is the main inhibitory neurotransmitter in mature neurons, but depolarizes immature neurons in the developing nervous system. GABA's depolarizing action during development is implicated in numerous aspects of circuit formation, in particular in glutamatergic synapse formation and refinement. Interestingly, during the height of gluatmatergic synapse formation in the hippocampus, GABAA transmission changes from depolarizing, to shunting, to hyperpolarizing. Thus, the question of timing is central when probing the role of GABAergic transmission in circuit development. We therefore asked the question, how does GABAA transmission regulate glutamatergic synapse formation as it shifts from being depolarizing to fully inhibitory. To do so we turned first to the organotypic hippocampal slice. Consistent with the literature, blocking hyperpolarizing GABA transmission for 48 hours in these cultures caused loss of dendritic spines. In contrast, blocking GABA transmission for 48 hours prior to the switch, when GABA is shunting, caused a marked increase in dendritic spines, synaptic proteins and mEPSC frequency. These changes lasted for up to a week following washout of the GABA blockade and were associated with elevated BDNF and cFos mRNA levels. Moving forward, to investigate whether this phenomenon occurs in the hippocampus in vivo, we have developed a panel of doxycycline-inducible GABA-disrupting plasmids for delivery via in utero electroporation.

1-A -14 1,2-dibromo-4-(1,2-dibromoethyl)-cyclohexane (TBECH) inhibits electrical activity of Purkinje neurons

Brittany Stojak[1], Rebecca van Ginkel[1], Tammy Ivanco[1], Gregg Tomy[1], Mark Fry[1]
[1]University of Manitoba

Brominated flame-retardants (BFRs) are environmentally pervasive and persistent synthetic chemicals that have been shown to disrupt neuroendocrine signaling and electrical activity of neurons. These observations have led to restrictions in the use of specific BFRs, and as a result, alternatives, such as 1,2-dibromo-4-(1,2-dibromoethyl)-cyclohexane (TBECH), have come into widespread use. TBECH has been reported to lack the toxicity of other classes of BFRs, however its safety is still questioned, as little is known of the neurological effects of TBECH. Therefore we carried out experiments to determine if TBECH could acutely alter electrical activity of neurons. Briefly, cerebella from e20 rats were dissociated and maintained for up to three weeks in culture. Spontaneous action potentials were detected by cell-attached patch clamp under control conditions for up to five minutes, then neurons were exposed to TBECH for one minute and allowed to recover in control solutions. Spontaneous activity of 15.5Hz was decreased by 73.8% (n=13) by 10uM TBECH, the highest dose tested. Lower concentrations of applied TBECH reduced activity in a dose-dependent manner with an apparent EC50 of 575nM: 1uM decreased activity by 68.0% (n=9), 100nM by 9.5% (n=6) and 10nM by 0.8% (n=8). These data indicate that acute TBECH exposure decreases spontaneous action potential firing in neurons and the altered activity may contribute to some of the observed toxic effects of TBECH.

1-A -15 The role of autophagy in the axonal growth and guidance of midbrain dopaminergic neurons

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Autophagy, a self-catabolic process by which cytoplasmic materials are degraded, have been shown to be important for neural development. We found here that autophagy achieves its highest levels at P7 and that autophagic protein LC3 is enriched in growth cones (GC) of midbrain dopaminergic (mDA) neurons. When neuronal primary cultures are incubated with guidance cues, strong autophagy induction can be seen as assessed by LC3-II western blotting. These data suggest a prominent role of autophagy during mDA neuronal development. To characterize the role of autophagy in mDA axon growth/guidance, we analyzed mutant mice in which the essential autophagy gene Atg5 is inactivated in mDA neurons (ATG5 cKO). mDA explants from ATG5 cKO mice show altered axonal morphology with GC enlargements, axonal swellings and decrease in the arborization complexity. These mice also show axonal profiles swellings and decreased number of axons reaching the striatum. Strikingly, when Atg5 cKO explant cultures are challenged with guidance cues important to mDA system development (Sema7a and Netrin-1), autophagy ablation leads to loss of reactivity to these cues.. Hence, our data shows autophagy as a key player in the maintenance of mDA axonal morphology and as a prominent effector downstream to guidance cues. Therefore, autophagy appears to play a central role in the mDA system development.

1-A -16 Mechanisms of Development and Protection of Neural Circuits

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We aim to understand the principles that regulate (1) the assembly of the nervous system during development and (2) the subsequent maintenance of neuronal architecture as the organism continues to develop and live. Whereas much research has identified key molecules that guide migrating neurons, how the cellular responses to the cues are orchestrated in time and space during development is unclear. Similarly, how the neural circuits established during embryogenesis are maintained throughout life, despite the addition of neurons into the existing circuits and the physical stress exerted by growth and body movements, remains largely unexplored. Our lab studies the cellular and molecular mechanisms by which neurons navigate in complex environments to reach their destinations, as well as the mechanisms ensuring the subsequent protection of neuronal structure and connectivity. We combine genetic, molecular, cell biological, and biochemical approaches using the powerful model organism C. elegans to address these questions. We will present our recent advances on the roles of heparan sulfate proteoglycans in modulating the cellular responses of migrating neurons to guidance cues. We will also discuss how the neuronal maintenance molecule SAX-7/L1CAM, and others, contributes to protecting neuronal architecture. Answering these questions are expected to have important implications for understanding the molecular mechanisms underlying neurodevelopmental disorders and neurodegeneration.

1-A -17 Can maternal antibiotherapy by ampicillin in group B Streptococcus-induced chorioamnionitis lead to newborn brain injury?

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Introduction: Group B streptococcus (GBS) is one of the leading microorganisms responsible for chorioamnionitis and preterm birth. A recent Cochrane database suggested an increase of neonatal

death and cerebral palsy associated with maternal antibiotherapy. Our hypothesis is that maternal antibiotherapy (ampicillin) following an end-gestational GBS infection triggers a maternofetal inflammatory response leading to placental and brain injuries in the offspring. Objective: Using an established rat model of GBS infection of the placenta, we will compare the maternofetal inflammatory response and the pattern of subsequent blood brain barrier injuries (albumin leak) underpinning neurodevelopmental impairments in the offspring exposed to gestational GBS ± antibiotic. Methods: At gestational day (G) 19, Lewis dams will undergo an intraperitoneal injection of 10^8 CFU of live serotype Ia GBS. Ampicillin will be given at 48 h and 60 h post-inoculation. Caesarean sections will be performed at G22. Results: Our preliminary results suggest an increase of pro-inflammatory cells' infiltration and cytokines' expressions in the placentas exposed to GBS + ampicillin, compared to sole GBS. We anticipate a more severe disruption of blood brain barrier within the fetal brains exposed to GBS + antibiotic compared to sole GBS. Conclusion: These results will provide the rational to design further preclinical studies aiming to test the placento- and neuro-protective roles of targeted anti-inflammatory treatments to prevent GBS-induced chorioamnionitis and inherent neuromorbidities.

1-A -18 Investigation of the role of p190RhoGAP downstream of the Netrin-1/DCC signaling axis in rat cortical development

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Axon pathfinding is a crucial point in the development of the Central Nervous System (CNS), where neurons use the distal tip of their axons-- the growth cone-- to navigate towards their final destination. The growth cone carries the machinery to respond to various guidance clues, one of which is netrin-1-- secreted, laminin-like protein. It signals through a cell membrane receptor protein-- deleted in colorectal cancer (DCC), to induce an attractive response. Mutations in DCC cause congenital mirror movement. Also, short nucleotide polymorphisms (SNPs) in the components of netrin-1/DCC signaling axis are related to neurological disorders such as schizophrenia, Parkinson's, aggressive behavior and Alzheimer. Despite its important role, today, our understanding of the netrin-1/DCC pathway is far from complete. Previous work from our lab showed that, through its SH2 domains, p120RasGAP is recruited to phosphorylated tyrosine residues on DCC (Tyr1361 and Tyr1418) upon Netrin-1 stimulation and regulates axon outgrowth and guidance. Interestingly, p120RasGAP can also interact with p190RhoGAP-- a 190KDa protein with intrinsic RhoGAP activity. It has already been showed that p190 is an important protein for CNS development as it is involved in fear memory formation, axon outgrowth and guidance; however, its role in Netrin-1/DCC pathway has not been addressed yet. In this research, using the combination of biochemical assays and fluorescent microscopy, as well as, isolated rat cortical neurons, we are dissecting the role of p190 in cortical neuronal development.

1-A -19 Developmental regulation of synaptic calcium dynamics in the prefrontal cortex.

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The ventromedial prefrontal cortex (vmPFC) plays a central role in higher cognitive functions in mammals. It is therefore important to uncover the mechanisms regulating the formation of these networks to pinpoint potential failures that could lead to the development of psychiatric illnesses such as autism and schizophrenia. Here, we combine whole-cell electrophysiology, two-photon calcium (Ca2+) imaging, and glutamate uncaging to examine fundamental features of synaptic Ca2+ dynamics during key epochs of PFC development and compared them to those occurring in the hippocampus. In the developing PFC, synaptic activation of NMDARs triggered long-decaying calcium signals that at times

invaded dendrites and propagated to nearby neighbouring synapses. These propagating signals were mediated by a NMDAR-dependent Ca2+-induced Ca2+-release (NMDA-CICR) mechanism. Intriguingly, the developmental trajectory was delayed in the PFC compared to the hippocampus, consistent with the reported generally slower maturation of this structure. Individual synapses that sustained these propagating Ca2+ events expressed hallmarks of less mature synapses: they displayed lower AMPA/NMDA (A/N) ratio and had shorter and stubbier spines. In keeping with the hypothesis that these propagating calcium signals may spatially regulate plasticity, we found that the variability of A/N ratios of neighbouring spines was lower within dendritic branches than within individual neurons. In sum, dendritic Ca2+ propagation may play a role establishing fine structural features of vmPFC connectivity.

1-A -20 Thyroid hormone: a key factor in neuromodulation of the respiratory network development

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Because thyroid hormones (THs) are present in the brainstem and are essential for both the differentiation of the presynaptic GABAergic neurons and the maturation of the postsynaptic components of the GABAergic system, we proposed that TH deficiency during gestation is sufficient to disrupt GABAergic modulation of the brainstem's respiratory network in newborn rats. Thyroid hormone deficiency in the foetus was recreated by administrating an antithyroid susbstance (Methimazole;MMI) to the pregnant dam from the first day of pregnancy (gestational day 1; GD1) to the day of experiment with the newborn. Fictive breathing from Sprague Dawley rats aged of 4 days was measured on an isolated brainstem-spinal cord preparation superfused with an artificial cerebrospinal fluid (aCSF). The output signal from the respiratory network was recorded by a suction electrode placed on the fourth ventral root representing the inspiratory signal sent to the diaphragm via the phrenic nerve. Compared to controls, pups from MMI treated dams showed 69% decreased phrenic burst frequency under baseline conditions. Moreover, they presented an increased dose-dependent depression of fictive breathing following Muscimol application (GABAA receptor agonist; dose 0.3µM) and increased elevation of phrenic burst frequency following Bicuculline exposure (GABAA receptor antagonist; dose 8µM). We conclude that TH deficiency results in an increased GABAergic inhibition in the core elements of the respiratory control circuit which could explain the reduced phrenic bursts frequency observed in the treated pups.

1-A -21 The association between physical activity, sedentary time and response inhibition in early childhood.

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Physical activity is associated with better response inhibition in middle childhood. However, few studies have used objective measures to examine this relationship in early childhood. Early childhood is a period of rapid development and when experiences are thought to have a greater impact on brain functioning. In this study, we investigated the association between physical activity, response inhibition and its neural correlates in a sample of 55 children (20 boys, 35 girls) aged 2.5 - 5.0 (M = 3.87, SD = .76). Children completed a preschool Go/No-go task measuring response inhibition while scalp EEG was recorded and for one week they wore an accelerometer that recorded their movement intensities in 15-sec intervals. Each 15-sec interval was classified as sedentary (<25 counts), light-intensity physical activity (LPA; 25 to ≤420 counts) or moderate- to vigorous-intensity physical activity (MVPA; >419 counts). Multiple regression analyses were conducted to examine if behavioural performance and event-related potentials associated with response inhibition (N2 and P3 amplitude) were predicted by

physical activity measures. Age and maternal education were included as covariates in the regression model. Results indicated that MVPA significantly predicted N2 amplitude on No-go trials and that the model accounted for 14.2% variance in the No-go N2 amplitude (R2=.14, F(1,51)=4.70, p<.05). Our finding suggests that MVPA predicts young children?s ability to effectively employ neural resources to perform the task and is consistent with findings reported in older participants.

1-B -22 Regulation of hippocampal network and memory by synaptic plasticity in somatostatin interneurons

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Long-term potentiation (LTP) is a prime candidate cellular substrate for learning and memory but remains poorly studied in inhibitory interneurons. We investigated the functional role of persistent Mechanistic Target Of Rapamycin Complex 1 (mTORC1)-mediated LTP in somatostatin interneurons (SOM-INs) in hippocampal CA1 networks and memory, by knocking out the expression of Raptor, an essential component of mTORC1, selectively in SOM-INs (SOM-Raptor-/- mice). Whole-cell recordings 24h after contextual fear conditioning (CFC) showed that training increased excitatory transmission and spine density at synapses onto SOM-INs from SOM-Raptor+/+ but not SOM-Raptor-/- mice, demonstrating that CFC induces persistent mTORC1-dependent LTP at excitatory synapses onto SOM-INs. Field recordings revealed upregulation of pyramidal cell Schaffer collateral pathway LTP by late-LTP induction in SOM-INs that is lost in SOM-Raptor-/- mice, indicating impaired regulation of CA1 network metaplasticity by SOM-IN LTP. SOM-Raptor-/- mice showed impaired long-term spatial and contextual fear memories but intact long-term cued-fear memory, indicating impairments in hippocampal memory. Mice with knock-down of the upstream repressor of mTORC1, Tuberous Sclerosis Complex 1 (TSC1), selectively in SOM-INs showed increased contextual fear memory, indicating that upregulating mTORC1 function in SOM-INs was sufficient to modulate hippocampal memory consolidation. Our results suggest that learning-induced persistent mTORC1-mediated LTP in SOM-INs regulates CA1 local network and hippocampal memory.

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

1-B -23 Role of basal pacemaker neuron activity in aversive long-term memory formation in Lymnaea stagnalis

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Learning and memory formation are critical physiological functions. There is increasing evidence that spontaneously active neurons possess distinct rules of activity-dependent plasticity as compared to quiescent neurons. In this study, we used a well-defined aversive learning model of aerial respiration in the mollusk Lymnaea stagnalis to study the role of spontaneously firing activity of the respiratory pacemaker neuron Right Pedal Dorsal 1 in aversive long-term memory (LTM) formation. We provide the first evidence suggesting that lower neuronal activity at the time of learning may be correlated with better memory formation in spontaneously active neurons. We also identified early functional predictors of aversive LTM formation that allowed us to characterize memory-specific and time-dependent changes in RPeD1 spontaneous firing activity during the memory consolidation process.

Taken together, our findings provide new insights into the diversity of cellular mechanisms underlying memory formation.

1-B -24 Inhibitory effects of dopamine on electrically coupled identified neurons

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Electrical coupling is mediated by gap junctions and promotes synchronous firing of connected neurons. The present study examines coupling between two identified cardiorespiratory neurons in the central nervous system of the pond snail, Lymnaea stagnalis. These neurons, designated as visceral dorsal 1 (VD1) and right parietal dorsal 2 (RPD2), innervate the heart and lungs and show synchronous 1-Hz firing. Previous work using hyperpolarizing current injections demonstrated that VD1-RPD2 coupling is asymmetric, being stronger from VD1 to RPD2. Here we employed pressure-ejected dopamine (an inhibitory neurotransmitter) to test asymmetrical coupling under more physiological conditions. We propose that dopamine may not only produce more realistic inhibitory coupling, but also provide evidence for distinct effects on network output. Focal application of 10-100 mM dopamine onto either neuron caused a 10-20 mV hyperpolarization and cessation of firing in both cells. Transfer of dopaminergic hyperpolarization from VD1 to RPD2 was more efficient compared to current injection (coupling coefficient of 0.9 vs 0.8). The response decreased when dopamine was applied at more hyperpolarized potentials (-50 vs -75 or -90 mV), suggesting inhibition is mediated by a potassium channel. In some instances, there was transient differential inhibition, where one neuron would spike while the other would fail to reach threshold. This disruption of network output may allow for desynchronization or functional decoupling, thus permitting these strongly connected neurons to temporarily act independently.

1-B -25 Mechanism of Pannexin Channel Mechanosensitivity

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Ischemic stroke driven cytotoxic edema expedites Pannexin-1 (Panx1) channel activation, facilitating chemotaxis-guided neuronal injury and death. Mechanisms underlying osmotic cell swelling induced Panx1 regulation are poorly understood. The objective here is to establish the contribution of F-actin and microtubules to swelling-induced augmentation of Panx1 channel activity in HEK293 cells stably expressing mouse panx1 (flag-mPanx1). In cells voltage-clamped at -60 mV, application of extracellular solution (ECS) with depreciating osmolarity induced a corresponding progressive magnification in Panx1 mediated currents. The effects of cytochalasin-D (CytD; F-actin depolymerizing drug) and nocodazole (NDZL; tubulin depolymerizing drug) were evaluated using immunofluorescence imaging and whole cell patch clamp recording. CytD not only inhibited the escalation in Panx1 channel response during osmotic cell swelling but also abated the basal channel activity [767 pA (control; n=7), 319 pA (treated; n=8)] indicating that F-acting contributes to cell swelling induced mechanosensitive as well as basal channel regulation. Tubulin disruption showed poor inhibition of channel activity augmentation during osmotic stress-induced cell swelling. Cells expressing Panx1 truncations at C-term (shown to interact with F-actin) further attest the decline in basal and stress-induced Panx1 mediated currents. To conclude, F-actin plays an important role in the augmentation of Panx1 channel activity during osmotic stress-induced cell swelling.

1-B -26 The stimulation of the shell part of the nucleus accumbens decreases sucrose intake in female rats

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Our laboratory has characterized a model of binge-like eating-prone (BEP) or -resistant (BER) female rats that mimic many of the clinical features of binge-eating disorders. When subjected to repeated stress episodes while having access to highly palatable food, BEP rats increased their sucrose consumption in response to stress. Some studies show that food intake can be reduced by stimulation of the shell part of the nucleus accumbens (NacSh) in male rats. The main objective of our study is, thus, to reverse the stress-induced binge-like eating phenotype by stimulation of the NacSh in BEP female rats. To start with, using optogenetics, we have studied the effect of the stimulation of this brain region on sucrose intake in female rats without binge-like eating phenotype. Sucrose intake, microstructure of licking and the c-fos expression were analysed. Stimulation of the NacSh resulted in a decrease in sucrose intake, in total licks number and in meal duration while there was no change in frequency or efficiency of licks in the female rats. Furthermore, c-fos expression was increased in the NacSh and decreased in the lateral hypothalamic area as well as in the rostral, but not the caudal part, of the ventral pallidum. In conclusion, this study has validated the fact that stimulation of the NacSh results in a reduction in sucrose intake in female rats. Thereafter, this experiment will be repeated on female rats with a phenotype of binge-like eating disorders to reverse the increase in sucrose intake observed during this behavior.

1-B -27 Characterization of Substantia Gelatinosa Neurons in Defined Medium Organotypic Cultures from "Tamamaki" GAD67-GFP mice.

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Defined medium organotypic cultures (OTC) of murine spinal cord can be used to study long-term modulation of synaptic activity and its relationship to chronic pain (Lu et al. Pain 121:261, 2006). We sought to determine whether the properties of substantia gelatinosa neurons of GAD67-GFP mice are preserved in OTC. Cultures were obtained from e12 embryos, treated briefly with an antimitotic cocktail and maintained in OTC for up to 6 weeks. NeuN staining of OTC showed that neuron number stabilized after 2 weeks in culture and remained unchanged for up to 6 weeks. GFAP staining for astrocytes increased with time but stabilized after 5 weeks in culture. 225 neurons were categorized according to their discharge pattern in response to depolarizing current as; Tonic (12.5% of population), Delay (1.5%), Transient (5%), Burst (48%), Initial Burst (10%), Gap-firing (7%), Phasic (8.5%) or Unclassified (5.5%; Cui et al., J. Neurophysiol. 105: 1102, 2011). These percentages were significantly different ($\chi 2$ test $P<0.001$) from those seen in acute slices (Boakye et al., this meeting). Despite this, it was noted that GABAergic (GAD67-GFP-expressing) neurons in OTC displayed a burst (60.23%) or tonic (12.5%) firing pattern as they did in acutely isolated slices (Boakye et al., this meeting). GAD-GFP neurons never expressed the delay firing pattern which, at least in rats, characterises excitatory neurons (Todd, Nat. Rev. Neurosci 11: 823, 2010). These data justify the use of OTC of mouse spinal cord to examine long-term modulation of inhibitory transmission in the context of chronic pain.

1-B -29 Mice are different from rats; characteristics of neurons in the substantia gelatinosa of the dorsal horn of Tamamaki GAD67-GFP mice

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Understanding the neuronal circuitry of the substantia gelatinosa (sg) is crucial to study of pain mechanisms. In rats, sg neurons exhibit 5 different firing patterns in response to depolarizing current; Tonic, Phasic, Transient, Delay or Irregular. Tonic cells have low rheobase and are often GABAergic whereas delay firing neurons are often excitatory (Todd, Nat. Rev. Rev, Neurosci 11: 823, 2010). These 5 categories do not adequately describe sg neuron types in the mouse. We categorized neurons in transgenic GAD67-GFP mice (Tamamaki et al., J Comp Neurol 467:60, 2003) as Tonic, Delay, Transient, Burst, Initial burst, Gap-firing or Phasic (Cui et al., J. Neurophysiol. 105: 1102, 2011). These accounted for 23%, 13%, 16.5%, 18%, 15%, 6.5% and 8% of neurons respectively. The burst category, which was not seen in rats, discharged tonically but had a high rheobase. As expected, GAD67-GFP was never found in delay cells but only 11% of GAD-GFP were tonic firing. The remaining GAD67-GFP neurons exhibited burst (22%), initial burst (22%), phasic (17%), transient (22%) or unclassified (6%) firing patterns. Unexpectedly, 39% of GAD67-GFP negative cells displayed a tonic firing pattern whereas some (13%) of GAD67-GFP negative cells displayed a delay firing pattern. Of the remaining GAD67-GFP negative neurons 17% expressed a transient firing pattern, 26% a burst pattern and 4% a burst pattern. Ongoing immunohistochemical studies of GAD65 and GAD67 distribution seek to determine whether the discrepancies reflect true differences between nociceptive processing in rats versus mice.

1-B -30 Constructing local field potential (LFP) models to decipher inhibitory cell type contributions during theta rhythms in CA1 hippocampus.

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Oscillatory LFPs are extracellularly recorded signal with frequencies of up to ~500Hz. They are associated with a number of physiological functions in health and disease and complement the information obtained by analysis of spikes. Because multiple neuronal processes contribute to the LFP, the signal is inherently ambiguous and more difficult to interpret than spikes. However, the biophysical origin of LFPs is well understood in the framework of volume conductor theory. "LFPy" is a python package that implements this framework and we have used it to construct a pyramidal cell model in CA1 hippocampus and generate extracellular potentials. Our pyramidal cell model receives inhibitory synaptic input from four different types of CA1 interneuron populations as taken from a previous, experimentally constrained inhibitory network model developed to understand theta (4-12 Hz) rhythms. We investigate the contribution of the different inhibitory cell types to the LFP. The contribution of each cell type is assessed during dynamic network interactions. We placed a virtual electrode probe along the vertical axis of the pyramidal cell to record its output in a layer dependent manner and were able to identify distinct regimes where specific cell type interactions distinctively affect the polarity, amplitude and frequency of the LFP signal. We further use independent component analysis (ICA) on our model LFP signal to quantify cell type contributions and make predictions on the underlying network interactions given experimental comparisons.

1-B -31 Role of kinase activity in modulation of inhibitory synaptic and extrasynaptic currents by neurosteroids

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Neurosteroids such as THDOC and pregnenolone sulfate (PS) are well known to modulate GABAA receptor activity. Tonic currents and mIPSCs were measured from pyramidal neurons (>14 days). Decay of mIPSCs were in two phases, fast decay lasting ~10 ms (τ1) followed by slow decay lasting ~50 ms (τ2). Neurosteroids alter mIPSCs by prolonging or shortening the decays. Previous studies have shown widely

varying effects of neurosteroids on GABAergic currents. We hypothesized that the variability is due to varying phosphorylation states of GABAA receptors. In this study, we have investigated the activity of THDOC on GABAergic mIPSCs and tonic currents after activation of various kinases. THDOC by itself caused shortening of τ1 and prolongation of τ2. It also greatly increased the negative charge transfer. Activation of PKC using PMA did not significantly alter the effects of THDOC. Treatment with THDOC after activation of PKA by forskolin resulted in two distinct populations of response. One population showed increased mIPSC amplitude. The other showed prolonged τ2 compared to the first population. TrkB activation by 7,8-DHF resulted in increased amplitude, but suppressed shortening of τ1 by THDOC. The combination of these outcomes, however, resulted in no change in the charge transfer. For tonic currents, THDOC caused a large inward shift in holding current, and thus increase in tonic inhibition. All three kinases suppressed the change in tonic current by THDOC. These data show that kinases differentially modulate the effects of THDOC on phasic and tonic GABA currents.

1-B -32 Voltage-Dependent Inhibition of Voltage-Gated Ca2+ Channels: Effects of Retinoid Signaling
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Retinoic acid, the active metabolite of Vitamin A, regulates cellular functions by binding to different classes of retinoid receptors, RARs and RXRs, capable of exerting genomic and nongenomic effects. A link between retinoid signaling and the activity of voltage-gated Ca2+ channels has previously been shown, but here, we demonstrate for the first time that an RXR pan-antagonist (HX531) produces voltage-dependent inhibition of neuronal voltage-gated Ca2+ channels. HX531 produced a significant decrease in voltage-gated Ca2+ current (carried by Ba2+), which was subsequently removed by a large depolarizing pulse. Upon activation of G-protein coupled receptors (and exchange of GDP for GTP), Gβγ subunits can produce such voltage-dependent inhibition of voltage-gated Ca2+ channels, an effect ubiquitous throughout the CNS. Because RXRs have previously been shown to associate with Gq in platelets and HEK cells, we aimed to determine whether this voltage-dependent inhibition by HX531 occurred via G-protein signaling. HX531 was applied in the presence of 10 mM GDP-βS (which blocks the exchange of GDP for GTP), but interestingly, this treatment did not prevent the voltage-dependent inhibition. This study supports a link between retinoid signaling and voltage-dependent inhibition of calcium channels and suggests it is not G-protein mediated, but rather involves a novel, as yet unidentified signaling pathway.

1-B -33 Numerical and morphological changes of microglia in the striatum of parkinsonian monkeys
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Parkinson's disease (PD) is characterized by the progressive loss of dopamine neurons located in the substantia nigra pars compacta, which innervates the striatum. This degeneration leads to a decrease of dopamine release in the putamen. In this study, post-mortem analyses of microglia were performed on healthy and PD female cynomolgus monkeys modeled by systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxin. Transverse sections taken through the striatum were immunolabeled with an antibody directed against the microglial marker IBA1 and subsequently analyzed by light microscopy. Quantitative analysis with an unbiased stereological approach reveals an increased microglial density in the putamen of MPTP monkeys, compared to control animals. Morphological analyses also show increased microglial cell body and arborization areas in the MPTP-intoxicated monkeys. Our findings indicate that microglia are recruited at neuronal microcircuits of the putamen following dopamine denervation. Based on these observations, we propose that microglia are involved

in the remodelling of neuronal microcircuitry that is known to occur in the striatum of these animals. Detailed ultrastructural analyses of microglial interactions with striatal afferent projections and comparisons between MPTP-intoxicated and controls animals will help to shed a new light on the role of microglia in the neuroadaptive changes that are known to occur in the striatum following the dopamine lesion that characterizes PD.

1-B -34 Information transfer at synapses formed by hippocampal mossy fiber on CA3 GABAergic interneurons

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Hippocampal microcircuits are composed of glutamatergic principal cells and GABAergic interneurons. The differential recruitment and local interactions of principal cells and GABAergic interneurons are thought to underlie information processing by the hippocampus. The hippocampal CA3 region receives strong excitatory afferents from granule cells which project their mossy fiber axons to contact both principal cells and interneurons. A single mossy fiber axon forms synaptic contacts on both principal cells and interneurons with strikingly different anatomical and functional properties. However, the principles of target-cell specific information coding remains unknown. Our previous results showed that giant mossy fiber terminals terminating on CA3 principal cells count the number of action potentials to transmit information. In contrast, it remains unknown how information transfer operates at synapses formed on interneurons. To investigate this question, we performed whole-cell patch-clamp recordings from visually-identified CA3 stratum lucidum interneurons. Our data suggest that glutamate release from mossy fiber terminals is facilitated during trains of action potential and is sensitive to the frequency of the bursts in a subset of interneurons, indicating a frequency-based coding principle for interneurons. Therefore, our results show a target-cell specific coding scheme.

1-B -35 The KChIP3 and ERK signaling pathway as components of the Cav3-Kv4 interaction

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Cav3-mediated calcium influx increases the Kv4 IA by right shifting the Kv4 half-inactivation potential (Vh) through a nanodomain interaction. We know that the Cav3-Kv4 interaction depends on the calcium dependent interacting protein KChIP3, but we do not know the molecular basis by which calcium signals a KChIP3-mediated change in Kv4 Vh. We conducted whole-cell voltage-clamp recordings in tsA-201 cells transfected with Cav3.1, Kv4.3, and KChIP3 cDNA, or a KChIP3 mutant construct lacking two calcium binding EF hand motifs (E186Q, E234Q). Blocking Cav3 channels with mibefradil (mib) produced a left shift of IA Vh in cells expressing wildtype KChIP3, but not in cells expressing the KChIP3 double mutant. Co-immunoprecipitation revealed an interaction between Cav3.1 and KChiP3 that was reduced in 0 calcium, suggesting a calcium-dependent association. Interrupting KChIP3 and Kv4 binding with a tat peptide also blocked the mib-induced IA Vh shift. Active ERK (phospho-ERK) was sufficient to left-shift IA Vh when intracellularly infused and phosphorylated both Cav3.1 and Kv4.3 on western blots. In contrast, infusing PD98059 to block activation of phospho-ERK occluded a mib-induced left shift in IA Vh. Together these results indicate that calcium regulation of Kv4 availability involves a new Cav3.1-KChiP3 interaction, depends on the integrity of the KChIP3-Kv4 interaction, and both the ERK signaling pathway and EF hand calcium-binding motifs of KChIP3.

1-B -36 Spatial reference memory impairments are associated with abolished CA1 theta-gamma cross-frequency coupling in freely behaving J20 APP mice

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Alzheimer?s disease (AD) has been associated with amyloid beta (Ab) aggregation, subsequent hippocampal neurodegeneration and memory defects. The exact nature and chronology of these pathological events remains largely unknown. Cross-frequency coupling (CFC), a physiological phenomenon that has been associated with memory encoding and retrieval, has been previously shown to be decreased in complete hippocampus preparations from 3 weeks old transgenic AD mice model. Several authors have proposed to segregate gamma band oscillations into slow (30-60 Hz), and fast (60-120 Hz) clusters that may rely on CA3 and medial entorhinal cortex inputs, respectively. In the present study, we have monitored CA1 local field potentials in the freely behaving J20 AD mice model (PDGF-APPSw, Ind) trained to seek a reward on a modified appetitive version of the Barnes maze as well as during REM sleep. At 6 months, J20 mice display more spatial errors as well as non-targeted exploration during the probe trial compared to non-transgenic (NTg) counterparts. Using a standardized measure of CFC, we show that theta-gamma CFC is significantly reduced during REM sleep, while it is abolished when mice actively explore the Barnes maze. Finally, we show that NTg mice display gamma oscillation dynamics (predominant fast gamma before reaching the target, followed by predominant slow gamma) that are abolished in J20 mice. This study suggests that circuits underlying cross-frequency coupling are affected very early in AD mice models, and might underlie the spatial memory defects

1-B -37 The role of microglia in remodeling of neuronal circuits in response to chronic restraint stress

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Microglia are extremely sensitive to chronic stress (CS) but their contribution towards brain and behavioral adaptation to CS still requires further investigation. Elevation of the stress hormone corticosterone promotes massive neuronal circuitry remodelling, however, how stress-induced changes in microglia mediate neuronal circuitry remodeling in stress-responsive brain regions is unknown. The aim of this study is to understand the effect of chronic stress on microglial functions in brain regions including the hippocampus (HPC), infralimbic cortex (IL), and basolateral amygdala (BLA). In our experiments, 8-12 week old C57BL/6J mice were subjected to chronic restraint stress (CRS) over a period of 10 days and assessed by a battery of behavioral tests, showing better short-term spatial memory and stronger social dominance. CRS-treated animals were also sacrificed for molecular analysis, and light and transmission electron microscopic analysis of Iba1-stained microglia from each region / animal. Following CRS, microglia show region-specific morphological changes (over-ramification in the IL and HPC and deramification in the BLA), ultrastructural changes in the BLA (more amoeboid, rounder process morphology, decreased process area and perimeter, increased circularity and solidity), an overall decreased MHCII+ (antigen-presenting) / CD206+ (scavenging) microglial ratio, and upregulation of microglial genes (C3, CD200r1, and glucocorticoid kinase Sgk1) but downregulation of P2ry12. These microglial changes after CRS may govern the adaptation of the brain and behavior to CS.

1-B -38 Functional cortical connectivity principles revealed by single-cell-initiated circuit tracing with rabies viruses

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Introduction: Individual cortical neurons can respond with remarkable selectivity to specific cues. In visual cortex, many neurons respond preferentially to specific orientations or directions of moving

images. How the feature selectivity of a single cell relates to its hundreds of nearby presynaptic neurons which span across cortical layers remains unclear. Furthermore, how the functional connectivity of the presynaptic network of individual neurons differs depending on the cortical layer in which they reside requires further study. Methods: We used in vivo 2-photon imaging to perform single cell electroporation to initiate monosynaptically-restricted, retrograde transsynaptic tracing with modified rabies viruses expressing GCaMP6s. We performed in vivo calcium imaging in mouse primary visual cortex to measure the visual motion evoked neuronal activity of individual pyramidal cells in either layer 2/3 or layer 4, as well as the activity of their presynaptic partners. Results: This single-cell-initiated circuit tracing technique labelled ~400 presynaptic cells connected to individual pyramidal cells in primary visual cortex. Most presynaptic neurons were located close to the postsynaptic 'starter cell', and presynaptic cells were located across all cortical layers. We investigated differences and similarities in presynaptic networks for individual neurons in layer 2/3 and layer 4. Conclusion: These results reveal the existence of different presynaptic network organization principles belonging to individual neurons both within and across layers in mouse visual cortex.

1-B -39 Postmortem characterization of cerebral vimentin expression and distribution in depressed suicides and healthy controls

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We recently reported that in the human brain, mRNA and protein expression of glial-fibrillary acidic protein (GFAP) in subcortical (caudate nucleus and mediodorsal thalamus) brain regions is significantly decreased in depressed suicides compared to matched controls, and that GFAP-immunoreactivity (GFAP-IR) presents major regional differences (Torres-Platas et al., 2016, Mol Psychiatry, 21:509-15). Here, we assessed in the same samples the regional expression and immunohistochemical distribution of vimentin, another intermediate filament protein expressed by astrocytes. Unlike GFAP, vimentin expression did not vary significantly between caudate and thalamus samples from depressed suicides and controls. Preliminary observations revealed that vimentin-immunoreactive cells also display distinct morphological and distributional phenotypes between cortical and subcortical brain regions. Experiments are currently under way to characterize the morphometric properties of these cells and to assess the degree to which GFAP-IR and vimentin-IR co-localize across brain regions. This work highlights unique cellular and molecular features displayed by human subcortical astrocytes and suggests that GFAP and vimentin are differently regulated in depression and suicide.

1-B -40 Role of calpain in activity-dependent translocation of CaMKII to synapses during synaptic potentiation

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Synaptic potentiation relies on NMDA receptor (NMDAR) activation and Ca2+ influx. Changes in cytosolic Ca2+ are detected by effectors such as calpain and CaMKII, transforming this information into signals inducing synaptic potentiation. Once activated, calpain cleaves many plasticity related proteins (PRPs), thereby remodeling the synaptic structure that might affect the activity and/or dynamics of many proteins. Meanwhile, CaMKII responds to Ca2+ by translocating to synaptic sites where it phosphorylates many PRPs, enabling synaptic potentiation. We aimed to investigate the relationship between the two proteins in the induction of plasticity. Inhibition of calpain activity in cultured neurons blocked ERK phosphorylation and insertion of synaptic AMPA receptors, two CaMKII-regulated processes involved in synaptic potentiation. Using time-lapse imaging we found that post-synaptic

CaMKII translocation is regulated by calpain activity. By performing Fluorescence Lifetime Imaging with a FRET based sensor of CaMKII activation, our findings indicate that calpain does not influence CaMKII activation. In support of this, our preliminary results indicate that calpain inhibition does not affect activity-dependent Ca2+ oscillations. These results not only further our understanding of the role of calpain in plasticity but also highlight the significance of the activity-dependent spatial redistribution of CaMKII. We are investigating further how calpain facilitates CaMKII translocation to synaptic sites.

1-B -41 Computational Modelling of AMPA receptors Trafficking at the Postsynaptic Density

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Integration of α-amino-3-hydroxy-5-methylisoazol-4-propionate (AMPA) receptors at the synaptic membrane plays an important role in synaptic plasticity and thus, in memory formation in the human brain. Traffic of AMPAR to the postsynaptic density (PSD) has been studied for many years, but its detailed mechanisms are still subject to controversies. To better assess current hypothesis on the matter, we suggest a simple mechanistic model of AMPAR trafficking to the PSD based on two main pathways : 1) lateral diffusion from the extrasynaptic dendritic membrane and 2) exocytosis from the spine cytoplasm. These reactions are implemented as a compartmental ODE model in the Virtual Cell software, where they are translated into mass action equations and Michaelis-Menten enzymatic equations. The model shows that the majority of the receptors are coming from lateral diffusion although relative importance of exocytosis increases with system stimulation, when mimicking induction of long term potentiation (LTP). This simple compartmental model has been expanded into a 3D spatial model with multiple PSD, spine and neck areas connecting on a common dendritic branch. Signalling pathways and their key proteins are included in this spatial mode to study their effect on AMPAR trafficking mechanisms. These interactions will be useful to further model synaptic cross-talk with neighbouring dendritic spines.

1-B -42 Neural correlates for the habituation of the hypothalamic-pituitary-adrenal axis to repeated stress

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Habituating to repetitive yet non-life threating stressors is instrumental for minimizing the negative consequences of chronic stress. Here, we report a neural correlate for the habituation of the hypothalamic-pituitary-adrenal (HPA) axis to repeated stress, which manifests as a decrease in the excitability of HPA axis output neurons [neuroendocrine neurons that express corticotropin releasing hormone (CRH) in the paraventricular nucleus of the hypothalamus (PVN)]. We obtained whole cell, patch clamp recordings from PVN-CRH neurons in slices from CRH reporter mice (male, 8-12 weeks old) subjected to daily 1-h restraint stress up to 21 days. We found that 21-day stress caused two mechanistically dissociable changes: 1) it delayed the time to elicit an action potential in response to depolarizing current injections, 2) it decreased the frequency of repetitive firing during long-duration current injections. Interestingly, the spike delay developed quickly and became evident as early as 1 and 7 day(s) of stress. This delay was reversed by 4-aminopyridine (4-AP, 5 mM), a voltage-gated potassium channel blocker. By contrast, the decrease of spike frequency only became evident after 21 days of stress, and was not reversed by 4-AP. The spike frequency decrease was negatively correlated with an increase in cell capacitance and whole-cell membrane conductance but not with unit membrane conductance. This points to stress-induced structural plasticity controlling the intrinsic excitability, and ultimately resiliency to chronic stress.

1-B -43 Mouse model of Fragile X syndrome has deficient inhibitory GABAergic plasticity

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Fragile X syndrome (FXS) is a neurodevelopmental disorder linked to deficits in several neurotransmitter systems. Dysfunction in both glutamatergic and GABAergic signaling are thought to play key roles in the manifestation of the disease, yet the exact nature of these defects is still emerging. Here, we identify a novel plasticity mechanism of inhibitory synapses in cerebellar molecular layer interneurons (MLIs) that is absent from FXS mice. We describe a novel activity-dependent plasticity triggered by NMDA receptors (NMDARs) which recruit α3-containing GABAA receptors (GABARs) into inhibitory synapses. Recruitment of GABARs required an elevation of cytoplasmic reactive oxygen species (ROS) and signaling through a protein kinase C/GABARAP-dependent pathway. Furthermore we show that excitatory input by NMDARs is diminished in FXS mice and consequently inhibitory synapse strengthening by α3-receptors is functionally lost. Since MLI connectivity is important in shaping Purkinje cell activity and consequently cerebellar output, our findings identify a disruption in synapse coupling in these neurons which adds to the growing body of evidence connecting cerebellar dysfunction to the pathophysiology of FXS.

1-B -44 Expression and localization of CB1R, NAPE-PLD, and FAAH in the nucleus accumbens of vervet monkeys

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Ventral tegmental area (VTA) dopamine release onto the nucleus accumbens (NAc) is central to the reward circuit, the dysregulation of which plays a role in addiction. The endocannabinoid (eCB) system, widely found in the central nervous system, may attenuate NAc GABAergic release onto the VTA, causing disinhibition of VTA-NAc dopamine release. In rodents, the cannabinoid receptor type 1 (CB1R), the synthesizing enzyme N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD), and the degradation enzyme fatty acid amide hydrolase (FAAH) are expressed in the NAc, but data for humans and monkeys are scarce. Using Western Blots and immunohistochemistry, we investigated the expression and localization of CB1R, NAPE-PLD, and FAAH in the NAc of the vervet monkey (Chlorocebus sabaeus). CB1R, NAPE-PLD, and FAAH were expressed across the NAc in the shell and core. CB1R is localized in Ctip2-positive cells, representing medium spiny neurons (MSNs), as well as in parvalbumin (PV)-positive cells, representing fast-spiking GABAergic interneurons. We observed complementary expression, but no co-localization, between CB1R and TH-positive cells, corresponding to dopaminergic projections from the VTA. Both NAPE-PLD and FAAH were also expressed in Ctip2- and PV-positive neurons, but not in TH-positive neurons. GFAP-positive astrocytes did not express CB1R, NAPE-PLD, or FAAH. These data indicate that the CB1R system is present in the monkey NAc and suggest that it may play an important role in the brain reward circuit through its influence on dopamine release.

1-B -45 Local and Long-Range Control of Astrocytes by Neuron-Derived Sonic Hedgehog

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Astrocytes play a critical role in maintaining optimal conditions for neurons and are involved in nearly all aspects of brain function. To faithfully fulfill diverse roles across the central nervous system, astrocytes display a complex range of phenotypes. Precisely how this astrocyte heterogeneity is created is poorly understood. By utilizing a combination of conditional mouse genetics, single-cell RNA sequencing, and electrophysiological recordings we found that Sonic hedgehog (Shh) is a neuron-derived regulator of the astrocyte transcriptome across multiple brain regions. Our results show that Shh signaling is both necessary and sufficient for regulating the expression of hundreds of genes, including several associated with human disease such as Slc1a3/GLAST and Kcnj10/Kir4.1. We are now systematically examining how subpopulations of neurons utilize Shh to modulate astrocyte function and influence local neural circuitry. Additionally, we are testing the hypothesis that projection neurons transport Shh over long distances to their target zones to influence the molecular properties of astrocytes. Overall, our findings demonstrate that astrocytes display remarkable plasticity in vivo and that neurons contribute to the specialization of astrocytes in the adult brain. Furthermore, this work shows that astrocyte properties are not solely established during development but instead rely on continuous access to local neuron-derived factors. This novel form of neuron-astrocyte communication has major implications for understanding mechanisms underlying brain health and disease.

1-B -46 Astrocyte-derived ACBP/DBI activates the hypothalamic melanocortin pathway to regulate feeding and energy homeostasis.

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Accumulating evidence suggests that hypothalamic controls of energy balance rely on metabolic sensing in astrocytes. However, the underlying mechanisms and role of astrocyte-derived signals remain elusive. Recently, we and others have shown that 1- Acyl-CoA Binding Protein (ACBP, also known as Diazepam Binding Inhibitor) regulates fatty-acid metabolism in astrocytes and 2- the octadecaneuropeptide (ODN), a secreted peptide derived from ACBP cleavage, inhibits feeding and improves peripheral glucose homeostasis. These effects of ODN are thought to involve the melanocortin pathway, a key player in the hypothalamic control of energy balance. We tested if astroglial ACBP acts as a gliotransmitter targeting anorectic proopiomelanocortin (POMC) neurons to in turn regulate energy balance. Using electrophysiological recordings and calcium imaging, we show that ODN selectively increases POMC neurons firing independently of GABAA inhibition and via a mechanism dependent on the ODN metabotropic receptor. In vivo, the anorectic and metabolic effects of ODN are blunted in melanocortin 4 receptor-deficient mice supporting that ODN central action is dependent on POMC neurons activation. Finally, mice with astrocyte-specific deletion of ACBP have increased food intake and reduced locomotor activity leading to increased susceptibility to diet-induced obesity. These findings highlight the importance of astroglial ACBP in the regulation of feeding through the melanocortin pathway and open new research avenues on the control of energy balance by hypothalamic gliotransmitters.

1-B -47 Long-term modulation of excitability by NMDA receptor signaling in cerebellar stellate cells

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[1]McGill University

The action potential (AP) is a fundamental signaling unit used by neurons to communicate within networks. The AP is generated through the interplay of several voltage-gated ion channel (VGIC) families, including Na+ and K+ channels, which determine threshold and frequency of firing. Although synaptic activity-driven changes in neurotransmission have been described throughout the brain, the

long-term influence of synapses on VGIC behaviour is less well characterized. We have observed a novel regulation of excitability in cerebellar stellate cells that involves NMDA receptor-mediated modulation of both Na+ and K+ channel activity. Local application of NMDA induced a persistent increase in spontaneous action current frequency during on-cell electrophysiological recordings. In whole-cell current clamp recordings, stellate cells exhibited a time-dependent increase in evoked AP frequency and hyperpolarization of spike threshold, both of which were eliminated by pharmacological block of CaMKII. To better understand the precise contribution of each VGIC family, a neuronal firing model was constructed and compared to experimental data. This revealed that the hyperpolarizing shift in stellate cell AP threshold can be primarily explained by changes in Na+ channel gating, while modulation of A-type K+ current and delayed rectifier K+ channels will affect spike frequency. Our work shows a novel modulation of Na+ channels by excitatory synapses, and provides insight into the role of NMDA receptor-dependent signaling in regulating inhibitory neuronal circuits of the cerebellum.

1-B -48 Matching electrophysiology to morphology in somatostatin-positive oriens-lacunosum/moleculare (O-LM) hippocampal interneurons

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Inhibitory interneurons of the hippocampus are critical controllers of network rhythms that are linked to learning and memory function. In particular, the oriens-lacunosum/moleculare (O-LM) cell directly regulates pyramidal cell activity in the CA1 region. Thus, it is essential to understand how the biophysical properties of O-LM cells, in conjunction with synaptic input, allow them to contribute to rhythms and function. Our previous models demonstrated that biophysical properties of O-LM cells affect output firing in specific ways. However, these previous models were developed using morphological and electrophysiological data obtained from different O-LM cells. To account for this mismatch, we performed a set of whole-cell recordings from O-LM cells in SOM-CRE/Rosa26YFP mice, followed by biocytin fills to match their electrotonic and morphological properties. We developed 3D reconstructions of the morphologies and fitted the passive properties of the resulting models using electrophysiological data from the same cells. Surprisingly, we found that the specific membrane capacitance (Cm) was substantially lower than reported previously in hippocampal cells. Furthermore, uniformly distributed specific membrane resistivity (Rm) values generated more optimal fits to the data relative to non-uniform distributions. Taken together, these results offer insights into the electrotonic structure of O-LM cells that affect synaptic integration and spiking output. These models will serve as a next generation of tightly constrained biophysical multi-compartment models of O-LM cells.

1-B -49 EVIDENCE OF A SYNAPTIC VESICLE BINDING SITE IN THE MIDDLE REGION OF THE C-TERMINAL OF PRESYNAPTIC CALCIUM CHANNELS

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Neurotransmitter release from synaptic vesicles (SVs) at fast transmitting synapses is gated by calcium ions that enter through voltage-gated calcium channels (CaVs, primarily CaV2.2 and 2.1) localized at the presynaptic membrane. There is a growing consensus that SVs are tethered to a CaV to permit gating by single channel Ca2+ domains (Stanley, Neuron 1993, TINS 2016), but the mechanism of this molecular link remains poorly understood. We developed an in vitro SV binding assay (SV-PD) to demonstrate that intact avian CaV2.2 and also the distal third segment of its long splice C-terminal (C3) can capture SVs (Wong et al., 2013). A palette of blocking peptides was used to identify the SV binding site as an HxxRR

motif just proximal to the C terminal tip (Gardezi et al., 2016). Recently, we observed that a fusion protein encoding only the proximal two-thirds of the CaV2.2 C terminal (C1-C2) could also capture SVs, suggesting a second binding site. In this study we explore the properties of this SV binding site in both CaV2.1 and CaV2.2. Since little molecular information is available on chick CaV2.1, we first cloned the full-length channel from chick brain cDNA. Wild-type and mutant C terminal fusion proteins identified an SV binding site in the middle, C2 region, of both channels that included several putative SV binding motifs. Preliminary data suggests that the C2 binding site has a higher affinity for SV binding than the previously reported CaV2.2 C3 region. This suggests that it may play a more important role in tethering SVs to the CaV during transmitter release.

1-B -50 Layer-specific calcium signalling and plasticity in dendrites of hippocampal fast-spiking interneurons

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In fast-spiking (FS), parvalbumin-expressing interneurons of the hippocampus, local postsynaptic calcium (Ca2+) nonlinearities through Ca2+-induced Ca2+ release can be elicited in distal basal dendrites and control the induction of long-term plasticity at excitatory synapses. However, recent research has suggested that apical dendrites may play a more active integrative role in FS interneurons by allowing the generation of dendritic Ca2+ spikes during periods of high frequency network activity . To clarify whether there are different modes of input-specific dendritic integration and synaptic plasticity in these cells, we further investigated the generation of postsynaptic Ca2+ transients at different dendritic locations by using two-photon Ca2+ imaging and local electrical stimulation and examined the summation of Ca2+ responses and associated changes in synaptic efficacy. We found that apical Ca2+ events induced by electrical stimulation summated supralinearly in a similar way to responses in basal dendrites. However, our results also indicated that local Ca2+ nonlinearities generated at excitatory synapses of apical dendrites could reliably induce a form of short-term potentiation that was not seen during stimulation of basal dendrites. This indicates that distinct plasticity mechanisms may be activated in a location-specific manner in the dendrites of FS interneurons. Overall, our results deepen the current understanding of how the dendrites of FS interneurons may integrate and modify incoming information from different inputs.

1-B -51 Mitochondrial Trafficking and Function in Cortical Astrocytes

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The central nervous system is the most energy expensive organ in the mammalian body. Remarkably, more than 90% of ATP produced by neurons and astrocytes is generated through oxidative phosphorylation in mitochondria making the CNS particularly dependent on their function. Mitochondria are highly dynamic organelles and are actively recruited to compartments with high energy-demand. Insufficient energy supply, due to dysfunctional or mislocated mitochondria has been implicated in a variety of neurodegenerative disorders, including Parkinson?s disease, ischemic injury, and ALS. The cellular role of mitochondrial transport and the molecular mechanisms involved have been intensely investigated in neurons, however, the properties of mitochondria in astrocytes remains to be better understood. Using in utero electroporation to express mitochondrially targeted fluorescent proteins in mouse astrocytes in vivo, we observed that mitochondria are distributed throughout the territory of astrocytes. However, not all distal astrocyte processes contain mitochondria suggesting specific targeting mechanisms are involved. To address this, we developed genetic tools to disrupt

mitochondrial transport in astrocytes in vivo. We found that disrupting particular mitochondrial trafficking proteins alters the positioning of mitochondria. Manipulated astrocytes displayed significant changes to their spontaneous Ca2+ activity. We are currently investigating how these changes in astrocytes impact neurons, synapses, and local microcircuits using advanced imaging and electron microscopy techniques.

1-B -52 THE CYTOKINE IL-27 SHAPES THE PROPERTIES OF HUMAN ASTROCYTES IN THE CONTEXT OF MULTIPLE SCLEROSIS

Florent LEMAITRE[1], Vincent Sénécal[1], Diane Bauseigle[1], Elie Haddad[2], Nathalie Arbour[1]
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Perturbed astrocyte functions have been associated to the pathobiology of multiple sclerosis (MS). In MS brains, astrocytes functions and expression profiles are altered but the exact impact of such alterations is still incompletely resolved. Interleukin-27 (IL-27) exhibits pro and anti-inflammatory properties upon binding to its receptor (IL-27R). We previously showed that human astrocytes in MS brain lesions and in-vitro can express both IL-27 and IL-27R. We demonstrated that IL-27 induces STAT1 phosphorylation but not STAT3 in human astrocytes. We speculate that local CNS IL-27 production alters numerous functions of astrocytes in MS brains. We observed that IL-27 triggers the NF-kB pathway in primary human astrocytes. IL-27 increases the expression of suppressor of cytokine signaling (SOCS) 1 and SOCS3 by resting astrocytes. In IL-1β-treated astrocytes, IL-27 augments SOCS1 but reduces SOCS3 protein levels. We also demonstrated that IL-27 enhances mRNA levels of two immunoregulatory molecules: PDL-1 and IL-10 and the secretion of key immune mediators sICAM and CXCL10 in both resting and inflamed conditions. Finally, we showed that IL-27 modulates the expression of key non-immune molecules expressed by human astrocytes. IL-27 upregulates mRNA levels of Cx43 and N-system amino acid transporter 1 (NAT1) and even counteracts the IL-1β-mediated down-regulation of these molecules. Our results support the notion that IL-27 alters both immune and non-immune functions of human astrocytes and that such impact could play a role in the brain of MS patients.

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these molecules. Our results support the notion that IL-27 alters both immune and non-immune functions of human astrocytes and that such impact could play a role in the brain of MS patients.

1-B -53 Stress Hormone CORT Induced Neuroplasticity in the Ventral Tegmental Area

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Chronic stress can affect mesolimbic dopamine system and cause anxiety and depressive disorders. However, the mechanism by which stress hormone alters neuroplasticity in the Ventral Tegmental Area (VTA) dopamine neurons is largely unknown. A mice model of stress is employed by application of the hormone corticosterone (CORT) in the drinking water for 1 or 7 days in the present study. Increased water and food intake, but decreased weight gain was observed in 7d CORT treated mice. Consistent with previous studies, plasma insulin was significantly increased in 7d CORT mice compared to vehicle controls. Using whole cell patch clamp, we recorded excitatory and inhibitory synaptic transmission onto VTA dopamine neurons identified with posthoc staining for tyrosine hydroxylase. 7d, but not 1d CORT mice had decreased frequency with no change in the amplitude in both mEPSCs and mIPSCs. Accordingly, glutamate release probability was decreased onto dopamine neurons of 7d CORT mice, measured by a paired pulse ratio. Insulin-induced long term depression of VTA dopamine neurons was absent in 7d, but not 1d CORT mice. Future directions will test if this impairment is due to occlusion by high insulin levels, elevated endocannabinoid signaling, or decreased existing release probability. Elucidation of neural mechanism underlying chronic CORT induced plasticity in the VTA dopamine neurons can provide potential therapeutic targets for chronic stress related disorders.

1-B -54 Identifying Critical Regulators of Dense Core Vesicle Trafficking and Fusion at Drosophila

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Regulated secretion in neurons occurs via two main classes of neurosecretory vesicles, i) synaptic vesicles (SVs) and, ii) dense core vesicles (DCVs). The fusion of SVs is a rapid and heavily regulated process coordinated by synaptic proteins that modulate docking, priming, and fusion. SVs, responsible for rapid communication involving the release of neurotransmitter molecules, are well characterized, and the molecular machinery underlying their fusion is fairly well understood. DCVs are responsible for the transport, storage, and release of proteins and neuropeptides at multiple cellular locations, and are known to be involved in a multitude of biological processes including synaptogenesis, synaptic transmission, synaptic plasticity, and others. Unlike SVs, DCVs require a much larger stimulus (30+ Hz stimulation) in order to trigger exocytosis and are therefore likely differentially regulated compared to SVs. Using tagged versions of DCV cargo and transmembrane components, we are beginning to investigate how DCVs are trafficked at the neuromuscular junction in Drosophila in order to illuminate the synaptic machinery that mediates trafficking and fusion. We are also employing quantal resolution imaging of vesicle fusion at individual actives zones to determine how DCV containing neuromodulators regulate synaptic communication.

1-B -55 BDNF plays a critical role in regulating GABAergic synapse function and morphology post-ischemic injury

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Ischemia is a neuropathological condition characterized by the deprivation of oxygen and glucose causing neuronal damage leading to changes in synaptic functions. One of the key molecules known to be involved after ischemic injury in synapse functional regulation is the neurotrophin. However, little is known about the role of brain derived neurotropic factor (BDNF) on inhibitory synapses under ischemic conditions. In non-pathological conditions, BDNF can modulate inhibitory neurotransmission such as GABAergic electrical activity and/ or expression of GABA A receptor (GABAAR) subunits. GABAARs mediate fast synaptic inhibition in the CNS and their density at the post-synapse is partly dependent of the scaffolding protein gephyrin. In the current study, we used the ischemic in vitro model oxygen-glucose deprivation (OGD) on organotypic hippocampal slice culture and focused on inhibitory synapses on CA1 pyramidal cells. OGD paradigm raised BDNF mRNA levels at 90 minutes and induced reduced GABAergic transmission and decrease expression of different GABAARs subunits and gephyrin. These effects could be prevented by blocking BDNF downstream signaling e.g TrKB, ERK and GSK3beta. Moreover, over-expressing gephyrin phospho-mutant blocked BDNF-mediated decrease in gephyrin expression. Taken together, the data highlight the important implication of BDNF in altering GABAergic synapses during ischemic injury.

1-B -56 Optical nanoscopy of the molecular mechanisms of neuronal development and plasticity

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The development of optical nanoscopy techniques that overcome the diffraction limit now allow to observe protein structures and dynamics at the scale in which they reside in their various cellular environments. One of these techniques, STimulated Emission Depletion microscopy (STED), is particularly well suited for live-cell imaging with a resolution down to 25 nm. It is very powerful for colocalization experiments since chromatic aberrations do not impair on the colocalization precision. Recently, a periodic lattice formed by spectrin and F-actin in both axon and dendrites was discovered with optical nanoscopy. Although its structure and modulation during development have been described, the functions of this cytoskeletal lattice remain unknown in neurons. With STED nanoscopy, we are imaging in live and fixed cultured hippocampal neurons the actin-spectrin lattice present inside dendrites and axons. To assess their regulation and function, we are manipulating the environment and expression of putative regulators in the cultures. We are using STED also to examine the dynamic remodelling of excitatory synapses at the molecular level. We combine different types of probes, such as nanobodies, SNAP-Tag, phalloidin-staining and live actin-staining to achieve the highest possible resolution for multi-color nanoscopy. This nanoscopy technique provides unprecedented details on the molecular cyto-architecture of neurons and synapses that will help understanding the spatio-temporal regulation of the molecular processes that support neuronal development and plasticity.

1-B -57 The effect of anti-VEGF and the kinin/kallikrein system on retinal inflammation in a rat model of laser induced choroidal neovascularization

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The neovascular aged-related macular degeneration (AMD), is the leading cause of legal blindness in the elderly. It is presently treated by anti-VEGF intravitreal injection in order to stop the neovascularization. In seeking of more efficient treatments to prevent retinal damage, it has been proposed that the kinin-kallikrein system (KKS), a key player in inflammation, could be involved in AMD etiology. However, the role of kinin receptors and their interaction with VEGF in AMD is poorly understood. In order to address this question, choroidal neovascularization (CNV) was induced in the left eye of Long-Evans rat. After

laser induction, anti-VEGF or IgG control were injected into the vitreal cavity. Alternatively, B1R antagonist R954 was topically administered twice day/10-days. Then, retina was processed to measure vascular permeability, leukostasis or identification of retinal inflammatory mediators. The number of labelled adherent leucocytes was significantly increased in laser-induced CNV compared to the control eye. This was significantly reversed by one single injection of anti-VEGF. Extravasation of Evans blue dye was significantly increased in laser-induced CNV eyes compared to control eyes and partially reversed by one single injection of anti-VEGF or by R954 treatment. The mRNA expression of inflammatory mediators was significantly increased in the retina of CNV rats. This study is the first to highlight an effect of the kinin/kallikrein system in a model of CNV that could be reduced by both anti-VEGF therapy and topically administered B1R antagonist R954

1-B -58 Comparison of Adult Human and Rat Spinal Cord Neural Stem/Progenitor Behavior

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Spinal cord (SC) injury recruits neural stem and progenitor cells (NSPCs), but they fail to restore functionality of the SC. These NSPCs can be modulated towards beneficial fates to promote neurological recovery in animal models. However, it remains unclear how efficiently human SC NSPCs can be modulated towards similarly beneficial fates. Using an in vitro assay, primary- and secondary-derived NSPCs (pd- and sdNSPCs) from human and rat thoracic SC were assessed for their behavior with 1%FBS and regenerative potential with the administration of exogenous factors in serum free media: EGF and FGF2 to induce proliferation, and RA, BMP4, or PDGF-AA to induce neural, astrocytic and oligodendrocytic fates, respectively. Cultures were treated for seven or 14 days, fixed, and then characterized by immuno-staining against cell specific markers, visualized by immunofluorescence, and quantified as a % of immuno-positive cells. Rat (n=3) pdNSPCs generated mostly astrocytes (71.8±5.6%) and to a lesser extent neurons (15.2±4.2%) and oligodendrocytes (2.82±1.3%), while human pdNSPCs (n=3) chiefly differentiated into neurons (68.5±16.9%) with little (<2%) gliogenesis. Rat NSPCs proliferated at a greater rate than human NSPCs (2.92-fold for pdNSPCs, and 3.66-fold for sdNSPCs). RA induced neural differentiation of human (2.2 fold) and rat (3.2 fold) NSPCs upon a 14 day treatment. Human and rat NSPCs differ in their proliferative index and differentiation profiles. This information may impact on the type and duration of potential NSPC therapeutic strategies that are translated to humans.

1-B -59 Fasting Induced Plasticity in Dopamine Neurons of the Ventral Tegmental Area

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Dopamine (DA) neurons in the ventral tegmental area (VTA) are critical for signaling environmental cues predicting motivationally relevant stimuli. Different metabolic states, such as hunger or satiety, can differentially modulate the activity and output of DA neurons. Chronic food restriction can increase excitatory synaptic strength onto DA neurons, but it is unknown how acute fasting influences excitatory synaptic transmission. Acute fasting is known to induce elevated corticosterone (CORT). Because CORT is known to influence endocannabinoid(EC) signalling in the hypothalamus, we hypothesized that acute fasting may alter EC modulation of excitatory synaptic transmission onto VTA DA neurons. Mice were fasted for 16h during the dark cycle, and midbrain slices from male or female mice were then prepared for whole cell patch clamp electrophysiology. We found that depolarization induced suppression of excitation (DSE) inhibited excitatory synaptic transmission similarly in non-fasted male and female mice. The CB1 antagonist, AM251, blocked this effect. However, fasted female mice had a significantly greater

DSE than non-fasted females, whereas there was no difference in DSE between fasted and non-fasted male mice. To determine the excitatory input suppressed by ECs, we compared DSE with optogenetic stimulation of lateral hypothalamic inputs to the VTA to local electrical stimulation of all excitatory inputs and found no significant difference. These experiments suggest that the mesolimbic dopaminergic output may respond differently to fasting in female compared to male mice.

1-B -60 Dynamic features and plasticity of quantal glutamate release at single hippocampal CA1 synapses

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Transmission at single synapses in the brain is stochastic, unreliable and variable. The full complement of factors that contributes to such synaptic noise, including their plasticity potential, still remains only partly understood. Here, we revisited, and expanded upon, key concepts of glutamate release at single dendritic spines of CA1 pyramidal neurons. Using whole-cell electrophysiology, two-photon imaging and glutamate uncaging, we show that the genetically-encoded optical glutamate sensor iGluSnFR is a linear reporter of glutamate concentration over a physiological range, with kinetics comparable to those of ionotropic glutamate receptors. Using this sensor as a means to carry out optical quantal analysis, we provide an estimate of the variability in cleft glutamate concentration at single synapses, and describe the ability of postsynaptic glutamate receptors to decode such variability. We also present experimental evidence for multivesicular release at CA1 synapses, and describe dynamical features of its occurrence. Lastly, we show that the amount of glutamate release is regulated during synaptic plasticity and can influence quantal size. Together, this work emphasises that the amplitudes of individual quantal events may be part of the informational content transmitted at central synapses.

1-B -61 Pan-neurexin perturbation results in compromised synapse stability and a reduction in readily releasable synaptic vesicle pool size

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Neurexins are a diverse family of cell adhesion molecules that localize to presynaptic specializations of CNS neurons. Heterologous expression of neurexins in non-neuronal cells leads to the recruitment of postsynaptic proteins in contacting dendrites of co-cultured neurons, implicating neurexins in synapse formation. However, isoform-specific knockouts of either all α- or all β-neurexins show defects in synaptic transmission but an unaltered density of glutamatergic synapses, a finding that argues against an essential function of neurexins in synaptogenesis. To address the role of neurexin in synapse formation and function, we disrupted the function of all α- and β-neurexins in cultured hippocampal neurons by shRNA knockdown or by overexpressing a neurexin mutant that is unable to bind to postsynaptic neurexin ligands. We show that neurexin perturbation results in an attenuation of neurotransmitter release that is in large part due to a reduction in the number of readily releasable synaptic vesicles. We also find that neurexin perturbation fails to alter the ability of neurons to form synapses, but rather leads to more frequent synapse elimination. These experiments suggest that neurexins are dispensable for the formation of initial synaptic contacts, but play an essential role in the stabilization and functional maturation of synapses.

1-B -62 Augmented stem cell potential in response to environmental enrichment is seen in juveniles but not adults

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Early in telencephalic development, neural stem cells are born in the ventricular zone and migrate through the cortex before differentiating into neurons and glia. Adult neurogenesis, however, is limited to specific niches in the brain: the dentate gyrus of the hippocampus (DG) and the subventricular zone (SVZ). The proliferation and differentiation potential of these neural stem cells is plastic and shows changes across states and in response to environmental manipulations. It has previously been shown that short-term environmental enrichment (Enr) is sufficient to increase the proliferation and differentiation of the GFAP+ stem cell pool in juvenile mice. Because longer-term Enr protocols are typically used to induce behavioural and functional recovery in adult mice, it is expected that that short-term Enr will be sufficient to induce an increase in neural stem cell potential only in juveniles. Using male C57 wildtype mice, we examined the potential of SVZ and DG NSCs in vitro following short-term Enr using neurosphere assays in both juvenile (P35) and adult (P90) mice. The assays were examined for NS number, size, and differentiation potential. We also examined changes in cognitive and anxiety behaviour. As hypothesized, we found that the short-term Enr increased learning and memory in juvenile mice, but not in the adult mice. These changes paralleled increased proliferation and differentiation of the stem cell pool in juveniles that was less pronounced in adults, suggesting developmental decreases in NSC potential in response to short-term environmental manipulations.

1-B -63 Gap junctions regulate nociception and synaptic strength of afferent input to the spinal cord dorsal horn

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Neuronal networks within the spinal cord dorsal horn regulate the transmission of sensory information. Gap junctions (GJs) containing the CX43 subunits are expressed by astrocytes in the superficial dorsal horn and have been implicated in the regulation of nociception. We explored the hypothesis that CX43-containing GJs regulate synaptic activity and plasticity to modulate nociception and pain sensitization. Synaptic activity was studied using in vitro spinal cord slices and spinal cord explants to measure extracellular postsynaptic field potentials (fPSPs) and miniature synaptic currents. We further tested the effects of intrathecal GJ blockers on mechanical nociception and hypersensitivity in vivo. At concentrations that inhibit CX43-containing GJs, application of either mefloquine or meclofenamate depressed evoked fPSPs in the superficial dorsal horn. This was accompanied by a phenotypic switch in synaptic plasticity in the dorsal horn, where low frequency stimulation induced long term depression rather than LTP of fPSPs. In whole cell recordings, CX43 blockade increased the ratio of synaptic inhibition to excitation in lamina II neurons. Finally, intrathecal administration of GJ blockers modestly impaired the mechanical nociception and hypersensitivity. These results demonstrate a role of CX43-containing GJs in regulating the strength and plasticity of primary afferent input to the superficial dorsal horn that may be distinct from their role in the modulation of excitatory synaptic transmission, and may underlie the behavioural effects of GJ blockers on nociception.

1-B -64 Presenilin1 M146V mutation inhibits chemical LTP induced AMPA receptor trafficking in cultured hippocampal neurons

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Mutations in presenilin 1 (PS1) are causative in early-onset familial Alzheimer's disease (AD). PS1 catalyzes the cleavage of the amyloid precursor protein generating amyloid β-peptide (Aβ). Although familial AD patients with PS1 mutations show severe amyloid pathology, mutant PS1 knock-in mice have memory deficits and learning impairment without amyloid pathology. Modifying synaptic strength is one of the major cellular mechanisms that underlies memory formation and is, in part, controlled by AMPA receptor trafficking. Exocytosis and membrane localization of AMPA receptors enhances synaptic transmission, whereas endocytosis of AMPA receptors reduces transmission. To investigate if mutant PS1 affects synaptic structure, we transfected PS1 wild type and PS1 M146V plasmids into rat hippocampal neurons. Using live cell immunostaining, we show that the PS1 M146V mutation decreases surface expression of both GluA1 and GluA2 AMPA receptors on dendritic membranes. Chemical LTP-induced AMPA receptor membrane trafficking, as measured by pH-sensitive GFP GluA1 and GluA2 chimeras, is attenuated in M146V expressing neurons. Furthermore, PS1 exists on the ER membrane and modulates spine calcium homeostasis. The Ca2 /calmodulin-dependent protein kinase II (CaMKII) pathway mediates receptor trafficking and we are currently testing the hypothesis that the PS1 M146V mutation affects receptor trafficking by altering this pathway. The present study indicates that PS1 may control synaptic plasticity via AMPA receptor trafficking.

1-B -65 Selective activation of large conductance calcium-activated potassium channels in dendritic spines from layer 5 pyramidal neurons

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Dendritic spines are the main receptacles of excitatory information in the brain. Their peculiar morphology, with a small head connected to the dendrite by a slender neck, has inspired theoretical and experimental work to try to understand how synaptic inputs are processed and stored in pyramidal neurons. The activation of glutamate receptors in spines triggers a large voltage change as well as calcium signals at the spine head. Thus, voltage-gated and calcium-activated K+ channels are good candidates to be located in the spine and to contribute to synaptic transmission. Here we study the presence and function of large conductance calcium-activated K+ (BK) channels in spines from layer 5 pyramidal neurons. We find that BK channels are localized to spines of different morphologies, but their activity - which reduces the amplitude of two-photon (2P) uncaging potentials - can only be detected in spines with small head volumes (< 0.1 um3). Numerical simulations predict that synaptic inputs impinged onto spines with small head volumes generate voltage responses and calcium signals that are significantly larger than those observed in spines with bigger head volumes, which successfully activate spine BK channels. Finally, using 2P uncaging of glutamate and 2P calcium imaging we find that calcium signals in spines with small head volumes are significantly larger than those observed in spines with big heads. These results suggest there BK channels are selectively activated in small head spines, which is likely of relevance for our understanding of synaptic processing in the brain.

C – Disorders of the Nervous System

1-C -66 Revealing microbiome-gut-brain interactions in opioid dependence

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Opioids are the gold standard in treating pain; however, their use is impaired by the development of tolerance and hyperalgesia when used chronically. Moreover, prolonged opioid use can lead to negative

affect that exacerbate the emotional disturbances already present in the chronic pain population. Recently, we have shown that inflammation in the brain contributes to this negative affect and opioid hyperalgesia, although the mechanism driving central inflammation remains unclear. Neuroinflammation has been shown to be influenced by disruptions to gut microbiota along a poorly understood gut-brain signaling axis. In this study, we hypothesize that opioid-induced changes in the gut microbiome contribute to neuroinflammation and subsequent behaviors. Male C57Bl/6J mice were treated with morphine over several days to induce tolerance and opioid hyperalgesia. 16S rDNA sequencing of fecal pellets from control and morphine treated mice was used to characterize commensal gut bacteria. Treatment with chronic opioids resulted in significant changes in the composition of the gut microbiota. Depletion of the gut microbiota with oral antibiotics induced neuroinflammation in the spinal cord and brain, and resulted in morphine tolerance, opioid hyperalgesia, and impaired reward behavior. Recolonization of the gut using fecal samples isolated from control, but not morphine dependent, mice restored behavior to control levels. These results indicate that the opioid-induced changes in the gut microbiota directly contribute to key behavioral phenotypes associated with opioid dependence.

1-C -67 Neural compensation in the recovery of a saccade selection bias after unilateral stroke in macaques

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Spatial extinction is an attention deficit commonly seen after a unilateral stroke and is characterized by impaired detection of a contralesional stimulus when an ipsilesional stimulus is presented simultaneously. This manifests as a disabling ipsilesional saccade selection bias that often only partially recovers over time. Here, we investigated longitudinal changes in whole-brain functional reorganization during recovery of the saccade selection bias following a right PFC stroke in macaque monkeys. We have experimentally induced a unilateral stroke in three macaque monkeys by injecting the vasoconstrictor endothelin-1 in right dorsolateral PFC and right frontal eye field, two oculomotor areas involved in saccadic eye movements. Saccade selection bias was measured in a free-choice saccade task in which the macaques were presented with two stimuli, one in each hemifield, with different onset asynchronies and were required to make a saccade to either one of the two stimuli. Following stroke, the animals exhibited a profound ipsilesional saccade selection bias that gradually recovered by week 16 post-stroke. We acquired resting-state fMRI at 7T pre-stroke and at week 1, 4, 8, 12 and 16 post-stroke. We applied graph theory to the functional networks and found increased network hub properties (degree, betweenness centrality) in bilateral caudate at week 16 post-stroke. This indicates that caudate increased its functional role as a "brain hub" at the time of recovery, suggesting a potential role in the compensatory mechanisms important for recovery of the saccade selection bias.

1-C -68 Chronic administration of pregabalin, a potential migraine therapy, alters hippocampal synaptic activity of severe familial hemiplegic migraine-1 mice

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Much of our current understanding of migraine comes from studies of familial hemiplegic migraine type-1 (FHM-1), a form of migraine with aura caused by mutations in the P/Q-type voltage-gated calcium channel. We are interested in the S218L human gain-of-function mutation underlying more severe FHM-1. Recent studies suggest that the pain drug pregabalin may have potential for treating migraine. Previous work in mouse knock-in models showed that spreading depression (SD), a hallmark of migraine

aura, invades CA1 hippocampus in FHM-1 mutants, but not wild type (WT) mice. We demonstrated that acute pregabalin exerted specific effects on SD and CA1 hippocampal synaptic activity in FHM-1 mice compared to controls. The current study investigated the effects of chronic (7-9d, 12mg/kg) pregabalin administered via a mini-osmotic pump on CA1 hippocampal synaptic activity. We established that chronic pregabalin produces similar effects on spontaneous excitatory postsynaptic currents (sEPSCs) as 100 µM acute pregabalin in FHM-1 mice causing an increase in sEPSC amplitude, but a decrease in frequency. In contrast, chronic pregabalin produces a decrease in sEPSC amplitude in WT mice whereas acute 100 µM pregabalin has little effect. Neither chronic nor acute 100 µM pregabalin alters sEPSC frequency in WT mice. These results show that in FHM-1 mice both chronic and acute pregabalin pre- and post-synaptically influence synaptic transmission in CA1 hippocampal neurons in a similar fashion. This work provides important insights into FHM-1 pathophysiology and pregabalin for treatment.

1-C -69 The pro-apoptotic role of Cited2 in stroke is functionally regulated by E2F1/E2F4

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We previously reported that the cell cycle related Cdk4-Rb pathway is essential for stroke induced death both in vitro and in vivo. However, the manner by which this signal induces death is unclear. Presently, we report that Cited2, a transcriptional coregulator, is dramatically increased following stroke/ischemic insult. Critically, utilizing conditional knockout mice, we show that Cited2 is required for death both in culture and in mice following ischemic insult. Importantly, we also determined the mechanism by which Cited2 levels are regulated. In this regard, we show that E2F family members participate in Cited2 regulation. First we show that E2F1 expression induces Cited2 transcription and that E2F1 deficiency leads to lower Cited2 expression. Moreover, we determined the potential E2F binding regions on the Cited2 regulatory sequence. We provide evidence that E2F1/4 bind to the Cited2 5' Untranslated Region using ChIP. We also show the functional outcomes of this interaction. E2F1 activates and E2F4 inhibits Cited2 transcription as revealed by luciferase reporter assay. We then identified the binding motif specific for E2F1, demonstrating that mutation of this site dramatically reduces E2F1-mediated Cited2 transcription. Finally, we demonstrate that E2F1/E2F4 regulate Cited2 expression in neurons after stroke-related insults. Taken together, these results demonstrate a critical stroke related pathway involving E2F family members and Cited2.

1-C -71 Concussion disturbs default mode network oscillatory coupling across multiple frequency scales

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Concussion impacts functional connectivity due to diffuse axonal injury, but the effect on neurophysiological 'intrinsic connectivity networks' (ICNs), such as the default mode, attention, visual, and motor networks, is unknown. We examined oscillations and synchrony following concussion in adults via MEG, focusing on ICNs. Resting data (5 minutes @ 600 Hz) was collected in 21 participants (all males, mean age = 31) with a single concussion in the acute/sub-acute stage of injury and a group of matched controls (all males, mean age = 27). A LCMV beamformer was used to derive time-series from coordinates that captured activity in 5 ICNs - the default mode, salience, dorsal & ventral attention, vision, and motor networks. Data were filtered in canonical frequency ranges (3-7, 8-14, 15-30, 30-55,

65-80 Hz) and functional connectivity was computed for all intranetwork source pairs using amplitude envelope correlations (AEC). No differences were found in the mean ICN power spectrum. Between-groups contrasts of connectivity revealed significantly increased coupling in the DMN and motor networks across alpha, beta and gamma ranges. This connectivity positively correlated with symptom severity - however, when anxiety and depression symptoms were accounted for, the association with motor network connectivity disappeared whilst the DMN correlation remained. These results suggest that even a single concussion can disturb the organisation of the DMN and motor network connectivity, but that elevated motor network coupling may be related to comorbid symptoms of anxiety and depression.

1-C -72 The expression of secretases enzymes in hippocampi of rats exposed to low doses of ozone

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Chronic exposure to low doses of ozone (O3) causes a state of oxidative stress which is involved in Alzheimer's disease (AD). The hallmark in the AD is the production and deposition of the ß-amyloid peptide 1-42 (Aß 1-42). The cut of ß-amyloid precursor protein (APP) by enzymes with ß (BACE1) and ? (PS1 and PS2) secretase activity produce the Aß1-42 peptide. However, the a-secretase enzymes (ADAMs) produce a peptide without pathological consequences. Our aim was to determine mRNA levels for APP and a, ß y ?-secretase enzymes in hippocampi of rats exposed to O3. We used male Wistar rats (n=72) separated into 6 groups (n=12). Each group received the following treatment: Control (air without O3); Groups 2, 3, 4, 5, and 6 were exposed to 0.25ppm of O3 for 7, 15, 30, 60, and 90 days respectively, for 4h daily. Six rats of each group were decapitated, the hippocampi were removed and processed for RT-PCR, and the rest of animals were deeply anesthetized and treated for immunohistochemical techniques. Results show that App mRNA levels do not have changes, the Adam9 and Ps1 levels diminish 50% during treatment, Adam10 decrease at 7 and 60 days 25%, and Bace1 only at 30 days in 15%. The Ps2 mRNA levels increase twice at 15 days of treatment. These results show that O3 exposure improves the amyloidogenic pathway and inhibits the non-amyloidogenic pathway since transcriptional levels contributing to the Aß1-42 peptide production. L.A.M-G is the recipient of a postdoctoral scholarship from Programa de Becas Posdoctorales, DGAPA UNAM. This study was supported by DGAPA JN221417 to S.R-A.

1-C -73 Mutations in the epileptic encephalopathy gene TRIO impair the prenatal and post-natal development of cortical GABAergic interneurons in mice

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Epileptic encephalopathies (EE) are neurodevelopmental diseases characterized by early-onset epilepsy with cognitive deficits that remain of unknown etiology in a majority of patients. Mutations in the TRIO gene have been recently identified using whole-exome sequencing in patients with EE or isolated intellectual deficiency. Trio has been shown to regulate the axonal guidance, dendritic development and lamination of hippocampal pyramidal cells. However, the roles of Trio in the development of INs are unknown. We performed a targeted repression of the Trio gene by ex vivo electroporation of a Dlx5/6::shRNA-tdTomato plasmid in organotypic cultures of e13.5 embryonic mice cortex. Using confocal and time-lapse imaging, we show that the repression of Trio in migrating cortical INs leads to increased cell body size and increased trailing and leading process length compared to INs electroporated with a control shRNA. These results also indicate that genetic repression of Trio alters

the migration dynamics of these neurons, suggesting that Trio is an important regulator of cortical INs during prenatal development. In addition, the early post-natal repression of Trio in cortical parvalbumin-positive (PV) INs by biolystic transfection of a 10kb-GAD67::shRNA in mice cortical organotypic cultures reduces the GABAergic innervation of pyramidal cells when compared to controls, suggesting an important role for Trio in the proper connectivity of PV INs. Altogether, these data suggest that TRIO-associated EE might be, in part, due to a defect in the early development of cortical INs.

1-C -74 Neuroprotective effect of the FTY720 in a mouse model of Parkinson's disease

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FTY720 and SEW2871 are two known sphingosine-1-phosphate receptor (S1PR) modulators, which have been shown to promote endogenous neuroprotective mechanisms. Whether they could prevent or halt dopaminergic (DA) neuronal death in Parkinson's disease (PD) has never been investigated. We studied the effects of FTY720 and SEW2871 treatments on the nigrostriatal loss and motor deficits induced by the administration of MPTP in mice. Chronic FTY720 and SEW2871 treatments were administered orally and began two days before the sub-acute MPTP treatments. Motor ability was evaluated and mice performances were altered at the beam and pole tests after seven days of MPTP administration. Deficits at the pole test were prevented by FTY720 and SEW2871 treatments. At the biochemical level, Western blot analyses revealed that striatal TH levels were decreased in MPTP-treated mice compared to control. These levels were upregulated in MPTP/FTY720 and MPTP/SEW2871 groups, relative to MPTP. In parallel, we observed an increase of striatal tumor necrosis factor alpha (TNF-α) levels in the MPTP-treated mice. This effect was prevented with FTY720 and SEW2871 treatments as a decreased was observed compared to MPTP group. Of note, administration of FTY720, SEW2871 and MPTP did not affect striatal levels of p-ERK 1/2 and sphingosine-1-phosphate receptor 1 (S1P1R). Altogether, our data suggests that FTY720 and SEW2871 treatments could prevent the motor deficits and neuronal insults induced by MPTP in mice. The mechanisms underlying these beneficial effects may include neuroinflammatory pathways.

1-C -75 Translational control of mood through phosphorylation of the eukaryotic initiation factor 4E

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The mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK) pathway controls mRNA translation, through the MAP kinase-interacting serine/threonine-protein kinase 1 and 2 (MNK1/2). MNKs phosphorylate the eukaryotic initiation factor 4E (eIF4E) in serine (Ser) 209. The MAPK/ERK pathway is involved in the pathophysiology of mood disorders, but the role of mRNA translation in depression remains unexplored. We investigated the phosphorylation levels of eIF4E in peripheral blood cells of major depressive disorder (MDD) patients and found them reduced in correlation with their depression score. Mice carrying the Ser209Ala mutation in the Eif4e gene (Eif4e ki/ki), as well as the Mnk1/2 double knockout mice (Mnk1/2 -/-), displayed several alterations relevant to anxiety and depression, including increased immobility in the forced-swim test, increased latency to feed in the novelty suppressed feeding; inhibited responsiveness to serotonin in the prefrontal cortex; and diminished activity of the dorsal raphe neurons. Lack of eIF4E phosphorylation led to reduced translation of the Nfkbia (IκBα) mRNA, a downstream increase in TNFα, and microgliosis, similar to MDD patients. The behavioural and serotoninergic alterations of the Eif4e ki/ki mice were ameliorated by

blockade of TNFα. These results provide evidence that dysregulation of MNK1/2-eIF4E signaling axis increases the susceptibility for depression by inducing TNFα, via impairment of IκBα translation and constitute the first evidence linking aberrant mRNA translation initiation to depressive disorders.

1-C -76 Microglial maturation and dysfunction in Huntington's disease

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Huntington's disease (HD) is a dominantly inherited neurodegenerative disease. It is a progressive disorder that affects a person's ability to control their movement, and affects cognition. The disease is caused by excess CAG repeats within the Huntingtin gene. These excess repeats cause the corresponding protein (HTT) to be misfolded and form aggregates within neurons in affected brain regions. There have been few studies on the role of glial cells in HD. We studied the maturation and dysfunction of microglia, the brain's resident macrophages, within the R6/2 model of HD. This model displays progressive motor deficits beginning at 6 weeks of age, and is incapacitated by 13 weeks of age. We studied microglial morphology, distribution, and maturity within the striatum of 3, 10, and 13-week old R6/2 vs aged-matched wild-type mice. At 3 weeks of age, prior to motor deficits, microglia in R6/2 animals have a larger arborization area and smaller morphological index, consistent with more mature microglia. While these changes normalized by 10 weeks of age, ultrastructural analysis using immunoEM revealed many changes. Microglial cell bodies (but not their processes) from R6/2 animals were more likely to contain phagocytic material. These data could indicate a proinflammatory state, as well as dysfunction within the phagolysosmal system. Furthermore, microglial processes in R6/2 mice were less likely to make contact with synapses and synaptic elements. These data indicate that microglia play an intimate role in HD pathogenesis and could be a target for therapeutic intervention.

1-C -77 Cdc25A is a critical mediator of ischemic neuronal death

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Increasing evidence suggests that cyclin-dependent kinases (Cdks) are inappropriately activated in mature neurons under ischemic stress conditions. We previously demonstrated a functional role for cyclin D1/Cdk4/pRb pathway in delayed neuronal death induced by ischemia. However, the molecular signal(s) leading to cyclin D/Cdk4/pRb activation following ischemic insult is presently not clear. Here, we investigate the cell division cycle 25 (Cdc25) dual specificity phosphatases as potential upstream regulators of ischemic neuronal death and Cdk4 activation. We show that a pharmacologic inhibitor of Cdc25 family members (A, B & C) protects mouse primary neurons from hypoxia-induced delayed death. The major contributor to the death process appears to be Cdc25A. shRNA mediated knockdown of Cdc25A protects neurons in a delayed model of hypoxia-induced death in vitro and global ischemia in the rat. We show that Cdc25A activity, but not levels, is upregulated in vitro following hypoxia and global ischemic insult in vivo. Finally, we show that shRNA to Cdc25A blocks Ser795 pRb phosphorylation. Overall, our results indicate a role for Cdc25A in delayed neuronal death mediated by ischemia.

1-C -78 Post-synaptic adhesion molecule Neuroligin-1 has a novel biomarker in Alzheimer?s disease

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In Alzheimer's disease (AD), synapse loss and neurodegeneration, partly caused by the neurotoxicity of soluble amyloid-beta oligomers (Aβo), are the best predictors of memory impairments. An important research area is to find early biomarkers affected by Aβo. Neuroligin-1 (NLG1) is a synaptic marker candidate since it was shown to be involved in cellular events altered in AD, such as synaptic plasticity and memory. A recent study showed that hippocampal injection of Aβ1-40 decreased NLG1 levels. However, the progression of this decrease remains unknown and we thus ignore if this event can be observed early in AD progression.We aim to determine if NLG1 may be one of the first molecules affected by Aβo and could be identified as a novel biomarker at the onset of AD. To do this, we have determined if NLG1 decreases early and progressively during chronic hippocampal injection of Aβ1-42 in mice and in primary cultured neurons exposed to Aβ1-42 for 6 to 72 hours. So far, we observed an increase in mRNA levels of two different Nlg1 transcripts after 2 days of hippocampal injection, and a trend towards a decrease in mRNA level after 4 days in several transcripts. Also, no significant changes in the protein levels have been observed. We are currently testing if Nlg1 KO mice have exacerbated neurodegeneration and memory deficits induced by chronic hippocampal injection of Aβ1-42, using Fluoro-Jade B staining, spatial object recognition and Morris water maze. This study has a strong potential to uncover NLG1 as an early biomarker of AD that might be targeted to develop new therapies.

1-C -79 Gene Regulation by Long Non-Coding RNAs in the Brain of Depressed Suicide Completers

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While various biological systems have been identified to be involved in depression, the mechanisms underlying their dysregulation remain unclear. Recently, a regulatory class of non-coding RNAs called long non-coding RNAs (lncRNAs) have been implicated in depression and their regulatory targets and mechanisms of action are now being uncovered. Here, we performed RNA-sequencing in the rostral anterior cingulate cortex of 26 depressed suicide completers and 24 matched controls. We identified 18 lncRNAs that were differentially expressed between depressed suicide completers and controls as well as putative protein-coding cis gene targets which also showed differential expression. Furthermore, using weighted gene co-expression network analysis, we have identified putative trans targets of these lncRNAs as well. After validating with RT-qPCR, we focused on 3 lncRNAs whose protein coding gene targets seem to be involved in interferon signaling pathways. We are currently investigating the function of these lncRNAs in cell models to confirm their regulatory roles on target gene expression. This work highlights the novel regulatory roles of lncRNAs in the brains of depressed subjects who committed suicide.

1-C -80 Strengthening Inhibition Can Rescue Neuronal Degeneration and Delay Motor Deficits in the ALS Mouse

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A balance between synaptic excitation and inhibition is essential for normal brain function. When this delicate balance is disrupted, it can lead to neuronal hyperexcitability, resulting in alterations in neuronal network activity and the onset of various neurological disorders. Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects both lower and upper motor neurons. While hyperexcitability is a hallmark feature during the pre-symptomatic stages of ALS, there has yet to be a systematic analysis of inhibitory synaptic function during the progression of this disorder. Thus, the main objective of this study is to determine if there is a reduction in inhibitory synaptic transmission in the primary motor cortex (PMC) during the pre-symptomatic phase of the disease, and if so whether

increasing inhibition delays the onset of symptoms and neuronal degeneration. Using biochemical and imaging techniques to examine the PMC, we found that various markers of inhibition were significantly compromised in the pre-symptomatic SOD1-G93A mouse. These reductions were correlated with a decrease in the frequency of spontaneous inhibitory postsynaptic currents. Using a combination of AAV-mediated genome engineering and Cre-mice cross-bred with SOD1-G93A mice, we chronically induced inhibition in the PMC during the pre-symptomatic phase. This strategy delayed the onset of neuronal degeneration and the associated motor symptoms in the SOD1-G93A mouse. Taken together, findings from this study could provide novel insights into the pathogenesis and treatment of ALS.

1-C -81 Characterization of recombinant human mitochondrial processing peptidase

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Mitochondrial processing peptidase (MPP) is a metallopeptidase that cleaves mitochondrial targeting signals from the majority of nuclear-encoded mitochondrial proteins. Mutations in both MPP and its substrates have been implicated in various neurodegenerative diseases, including Parkinson's disease (PD) and non-progressive cerebellar ataxia. One of these implicated substrates is PINK1 - a kinase whose mutations are known to cause early-onset autosomal PD. In healthy mitochondria, PINK1 is constitutively imported, cleaved first by MPP, and then retrotranslocated to the cytosol for proteasomal degradation. In this regard, MPP acts as a key junction for PINK1 import, proteolysis, and overall mitochondrial quality control. However, both the MPP cleavage site on PINK1 and its binding conformation remain unknown. To gain insight into the proteolytic mechanisms concerning PINK1 and other disease-implicated substrates, we have begun to characterize the human MPP heterodimer. We demonstrate that the human MPP dimer can be successfully purified from a co-expression system in E. coli. We have also developed a proteomics-based method to monitor MPP activity, using a synthetic presequence from malate dehydrogenase as a positive control. Research into the PINK1 cleavage site and mechanism of cleavage are currently ongoing in our laboratory.

1-C -82 Collapsin Response Mediator Protein 4 (CRMP4) regulates neuronal regeneration and degeneration after peripheral nerve injury

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Damaged neurons in the peripheral nervous system (PNS) have the potential to regenerate and reinnervate their targets, but this recovery is often incomplete as neuronal growth can be slow and hampered by extensive damage. Thus, it is critical to investigate the mechanisms underlying axonal regeneration to promote recovery after PNS injury. We are investigating the roles of Collapsin Response Mediator Protein 4 (CRMP4) in the neuronal response to injury. CRMP4 is a cytosolic phosphoprotein that regulates cytoskeletal dynamics during development to promote axon growth. It also impairs regeneration in the central nervous system, but its roles in the PNS are still unknown. We found that the different CRMP4 isoforms are spatially and temporally regulated following sciatic nerve injury. In the distal nerve end, calpain-mediated cleavage of CRMP4a occurs early after injury. The fragments generated impair neurite outgrowth and could be associated with neuronal degeneration. Also, in both the proximal and distal nerve ends, the level of CRMP4b is increased and could be associated with a growth-promoting role. Surprisingly, CRMP4 deletion impairs regeneration of sensory neurons and preliminary results indicate that it could also limit axotomy-induced degeneration. Thus, specific CRMP4

isoforms might be essential for the neuronal response to injury and we are further investigating their roles to elucidate a potential role in the coordination of degeneration and regeneration after PNS injury.

1-C -83 The neuroinflammatory process across the lifespan of Down Syndrome individuals

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Down syndrome (DS) individuals are at increased risk of developing early onset Alzheimer's Disease (AD). Given the triplication of chromosome 21, people with DS show an age-dependent intraneuronal accumulation of Amyloid-Beta (AB) (Busciglio, 2002) which develops into an advanced AD-neuropathology and, in most cases, dementia. We have earlier reported that early intraneuronal accumulation of AB unleashes a toxic pro-inflammatory process in a transgenic rat model of AD-like pathology (Hanzel, 2014). In light of this, we hypothesized that early AB accumulation in DS individuals will promote an early pro-inflammatory process in AD-asymptomatic DS individuals. To address this, we will study the expression of pro-inflammatory molecules and inflammasome activation throughout the lifespan of DS individuals. A qPCR array (QIAGEN) for classical inflammatory and inflammasome-related genes was performed in postmortem frozen frontal cortex tissue of DS infants, DS-adults and their age matched controls. Individual qPCR analysis was performed in the adult population. Our initial results in DS infants suggest an upregulation of pro-inflammatory factors IL-1B, IL-33, IL-6, IL-12a, IL12b, MCP-1, caspase-1 and 5, NLRP3, NLRP4. A downregulation of IFN-B and CARD18 was also observed. While DS-adults also show an upregulation of some of these molecules (IL-6, IL-12, caspase-1, NLRP3) the fold change was more substantial in DS-infants. These results suggest the existence of two different neuroinflammatory processes in the continuum of the AD neuropathology in DS.

1-C -84 The regulation of NMDAR and mGluR5 by microRNA-128-3p with relevance to neurodegenerative disease.

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Objective: To identify the functional targets of microRNA-128-3p , a miR that is deregulated in multiple CNS neurodegenerative diseases. Methods: First, the deregulation of miR-128-3p in CA1 neurons during RML Scrapie prion disease was identified using laser capture microdissection and real time PCR. Bioinformatic analysis was performed using miR-mRNA prediction algorithm TargetScan Human 7.1 to determine neuronal 3` UTR targets, which were validated by Luciferase Reporter Assay. The glutamate signaling pathways were manipulated in murine primary hippocampal neurons (hcc) to study the effects on miR-128-3p expression. Finally, miR-128-3p gain of function experiments were performed in hcc to determine effects on 1) mRNA targets using real-time PCR, and 2) protein changes using mass spectrometry. Results: In the CA1 hippcampal neurons, miR-128-3p is upregulated during early RML Scrapie and downregulated at symptomatic stages of disease. The predicted 3` UTR targets of GRIN2B, GRIN2D, and GRM5 were validated by Luciferase assays, and GRIN2D and GRM5 mRNA decreased during gain of function studies. In hcc, chronic synaptic and extrasynaptic NMDAR activation resulted in miR-128-3p reduction. Finally, the proteomic targets of miR-128-3p remained elusive as only 1 protein, SLIT3, was identified as downregulated by TMT mass spectrometry in miR-128-3p gain of function experiments in hcc. Conclusions: In hcc, mRNA encoding glutamate receptor subunits GRIN2B, GRIN2D, and GRM5 are regulated by miR-128-3p, and glutamate signaling overactivation results in miR-128-3p downregulation.

1-C -85 IL-1 alpha delivery in the CNS of mice induces death of mature oligodendrocytes

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Over 4 million people suffer from spinal cord injuries (SCI) worldwide, and about 200,000 new injuries occur annually. At the site of trauma, SCI causes direct damage to cell bodies of neurons and glial cells. This is followed by a second wave of tissue degeneration characterized by the death of oligodendrocytes (OLs) and subsequent demyelination of axons that survive the initial trauma, thus resulting in an amplification of the motor and sensory deficits. We recently demonstrated that dead and dying microglia at sites of SCI rapidly release the danger signal interleukin (IL)-1α, which in return triggers neuroinflammation. Accordingly, mice lacking the Il1a gene have an impaired inflammatory response and recover faster and to a greater extent than control mice after SCI. Here, we further investigated the role of the proinflammatory cytokine IL-1α in secondary cell death and CNS damage. Naïve (uninjured) C57BL/6 mice were injected in the cisterna magna with either 5 µl of PBS, IL-1α or IL-1β and then killed at 4 or 24 hours following treatment. Results showed that intrathecal delivery of IL-1α, but not IL-1β, induced death of mature OLs as early as 24 hours post-injection. Notably, IL-1α treatment also caused neuronal activation throughout the entire mouse spinal cord, as well as the activation of microglia and infiltration of innate immune cells in the perivascular space of spinal cord blood vessels. All together, our data suggest that IL-1α released by microglia after SCI may regulate OL cell death and demyelination.

1-C -86 Prevention of the collapse of pial collaterals by remote ischemic perconditioning during acute ischemic stroke

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Collateral circulation is a key variable determining prognosis and response to recanalization therapy during ischemic stroke. Remote ischemic perconditioning (RIPerC) involves inducing peripheral ischemia (typically in the limbs) and may reduce perfusion deficits and brain damage due to cerebral ischemia. Here, we directly investigated pial collateral flow augmentation due to RIPerC during distal middle cerebral artery occlusion (MCAo) in rats. Blood flow through pial collaterals between the anterior cerebral artery (ACA) and the MCA was assessed in male Sprague Dawley rats using in vivo laser speckle contrast imaging (LSCI) and two photon laser scanning microscopy (TPLSM) during distal MCAo. LSCI and TPLSM revealed that RIPerC augmented collateral flow into distal MCA segments. Notably, while control rats exhibited an initial dilation followed by a progressive narrowing of pial arterioles 60 to 150-min post-MCAo, this constriction was prevented or reversed by RIPerC. This prevention of collateral collapse was associated with significantly reduced early ischemic damage. Development of optimal approaches to non-invasive RIPerC may be neuroprotective during ischemic stroke while also augmenting recanalization therapies by improving blood flow in penumbral tissue. Further, identification of the blood borne mediators that maintain tissue viability and prevent collateral failure may lead to new pharmacotherapies for stroke.

1-C -87 Head Movements During Locomotion in Vestibular Schwannoma Patients: Decreased Variability After Unilateral Vestibular Lesion

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The vestibular system is vital for maintaining balance and stabilizing gaze, by detecting head motion and then generating the appropriate reflexes. It is well known that unilateral vestibular loss, results in

impaired balance and gaze control. However, much less is known about the effects of vestibular loss on voluntary behavior. Here, we analyzed locomotive behavior in vestibular schwannoma patients who had undergone a primary surgical resection of their tumor via suboccipital craniotomy and retrosigmoid approach with sectioning of the vestibular nerve. Head movements were recorded before the surgery, as well as two and six weeks after surgery using an inertial sensor (Carriot et al., 2014), which measures three-axis linear acceleration as well as three-axis of rotational velocity. Patients were asked to complete the Functional Gait Assessment, and we focused our analysis on short gait tasks including: normal walking, walking with eyes closed, and walking backwards. We quantified asymmetry, speed, and variability of gait and compared pre- and post-operative results to determine how patients' movements were altered. Notably, we found no significant changes in movement asymmetry. However, we found that even though locomotor speed decreased two weeks after surgery, it actually increased six weeks post-surgery. Furthermore, in contrast with previous studies, our results showed that the movement variability was lower after the surgery, and that this variability can be an important indicator of how patients adapt to altered motion and their recovery process.

1-C -88 The Christianson Syndrome Mutation NHE6 ΔES Impairs the Structure and Plasticity of Hippocampal Pyramidal Neurons

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Christianson Syndrome, an X-linked neurodevelopmental disorder, is characterized by intellectual disability, epilepsy, and autistic features. It is due to mutations in the SLC9A6 gene encoding sodium/proton exchanger NHE6, which localizes to early and recycling endosomes to regulates their luminal pH. We previously reported that in hippocampal neurons, NHE6 localizes to excitatory synapses, colocalizes with a subset of glutamatergic AMPA receptors (AMPARs), and is modulated by activity. However, the way that clinical mutations in NHE6 impair learning and memory is unknown. To this end, we are investigating how a prevalent NHE6 mutant, with deletions of Glu287 and Ser288 (NHE6 ΔES), can affect synaptic structure and plasticity. Expression of NHE6 ΔES into primary hippocampal neurons decreased dendritic branching and the density of dendritic spines, the postsynaptic sites of excitatory synapses. NHE6 ΔES further prevented spine enlargement and AMPAR insertion into synaptic sites following long-term potentiation (LTP). Compared to wild-type NHE6, NHE6 ΔES also showed reduced colocalization with early and recycling endosomal markers yet increased colocalization with markers for late endosomes and lysosomes, suggesting a mistargeting to lysosomes. Addition of a lysosomal inhibitor rescued dendritic spine density, AMPAR trafficking, and the structural response to LTP in NHE6 ΔES-expressing neurons. Overall, we find that NHE6 ΔES disrupts AMPAR trafficking during LTP, which may be the cause of learning and memory impairments in Christianson Syndrome patients with this mutation.

1-C -89 High-frequency deep brain stimulation of the fornix improves memory consolidation and causes network-level neuroanatomical remodelling in an Alzheimer's mouse model

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Deep brain stimulation (DBS) involves the targeted delivery of high-frequency electrical stimulation to brain regions affected by neuropsychiatric disorders using a surgically implanted electrode. Here we study the longitudinal effects of fornical DBS on brain structure and behaviour using a mouse model of Alzheimer's disease. 24 week-old male and female 3xTg mice were then implanted +/- 0.75 mm bilaterally, perpendicular to the skull plane at bregma, and at a depth of 3.25 mm to target the body of

the fornix. Sham (n = 4M/4F) or monophasic stimulation (n = 3M/4F) was delivered for 1 hour at settings homologous to those used in humans: 100 Hz, 100 μA, ~1.5 V with pulse width of 100 μs. Memory and cognitive flexibility was assessed weekly in a longitudinal water maze with changing platform positions. MRI image acquisition occurred 3 days before stimulation, 3 days and 6 weeks post stimulation. During weeks 3-4 post stimulation, animals showed a significant (P=0.013) bias to return to the previous week's platform position. Deformation-based morphometric analysis revealed significant (FDR 5%) relative growth of the anterior thalamus and hippocampus after 6 weeks in stimulated animals. Our findings suggest that acute DBS of the fornix enhances memory consolidation and makes memories harder to extinguish 3-4 weeks post stimulation. This may be mediated by remodelling of the anterior thalamus and hippocampal formation.

1-C -90 Neuroprotection and differential Na+/K+ pump isoform production in higher and lower brain regions

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Higher gray matter is more susceptible to acute ischemic injury than the lower brain. Discovering mechanisms contributing to the brainstem's resilience may inform targets for improved survival of higher brain regions. Our data mining suggests that the Na+/K+-ATPase 1a3 isoform is expressed in higher proportion in brainstem under basal conditions. It also pumps more efficiently under ischemic conditions than the 1a1 isoform which predominates in higher brain regions. We hypothesize that Na+/K+ pump isoform expression helps contribute to a region's susceptibility or resiliency to ischemia. Data from the Allen Brain Bank show proportionally greater 1a1 expression in higher brain regions. In support, our qPCR experiments in naive mice show proportionally greater 1a3 mRNA expression in brainstem and a higher proportion of 1a1 in neocortex. We analyzed 60 brain samples from 20 mice and found 1a3 mRNA expression was on average 2x higher than 1a1 in brainstem. In contrast, 1a1 mRNA expression was on average 2.2x higher than 1a3 in neocortex. Our parallel protein expression studies are consistent with these findings. We are following up these results with analysis of 1a1 and 1a3 mRNA and protein levels from a chronically-stressed cohort of mice. An additional cohort will undergo focal stroke. We suspect 1a3 expression will increase in the neocortex of behaviorally stressed or stroked mice. Understanding how Na+/K+-ATPase isoforms differ in their production in response to metabolic stress should yield insights into how such differences protect neurons during metabolic stress.

1-C -91 Stimulants consumption in a Canadian undergraduate student sample: prevalence and motives for taking illicit or low-dose prescription stimulants

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Stimulants drug use is reportedly on the rise among post-secondary students in North America; however, prevalence estimates vary widely (Wilens et al, 2008; Kudlow et al, 2013) and few studies have investigated students' motives for taking various stimulants. We examined self-reported stimulant use, including illicit stimulants like amphetamine and cocaine as well as low-dose stimulants prescribed for attention disorders, in a sample of undergraduates (N =289, 60% female, mean age 20.8 years) from a Quebec university. Among students surveyed, 17.6% had taken illicit stimulants and 16.3% had taken low-dose stimulants at least once in their lifetimes. Male students were more likely to have taken illicit stimulants ($\div^2$ (1) = 6.03, $p<0.05$); however, age, perceived academic performance, perceived stress level, anxiety, or depressed mood did not predict likelihood of use. Whereas motives for taking illicit

stimulants included "to have fun/get high" (94.1%), "to feel more energetic" (15.7%), and "to fit in socially" (9.8%), motives for low-dose prescription stimulants were more varied: "prescribed it for medical reasons" (40.4%); "to improve my academic performance" (55.3%); "to have fun/get high" (19.1%); "to feel more energetic" (14.9%). When asked if taking stimulants gives one an academic advantage, 20.5% indicated yes, whereas 27.5% indicated 'yes but only in the case of prescription stimulants'. These data contribute to a clearer picture of the prevalence of and attitudes toward stimulant use in undergraduate Canadian students, and may inform interventions in reducing use

1-C -92 Cuprizone-induced oligodendrocyte loss and iron overload

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The copper chelator, cuprizone (CZ), induces oligodendrocyte (OL) death and demyelination in the CNS, seen particularly well in the corpus callosum. As this chelation, would reduce availability of copper for copper-containing enzymes, particularly those involved in cellular iron efflux, we reasoned that CZ treatment would alter iron homeostasis and lead to iron accumulation that may be the cause of OL death. Also, iron is needed for remyelination, so one may expect to see an increase during the remyelination phase. In this study, we assessed the loss of mature OL and oligodendrocyte precursor cells (OPCs) from 2 to 5 weeks after start of CZ treatment, and correlated this with changes in expression of ferritin, a surrogate marker for cellular iron. The number of OPCs showed loss at 2 weeks followed by a gradual increase of ~ 2.5-fold at 5 weeks. Total number of OPCs and OL also showed a sharp loss at 2 weeks followed by a 3-fold increase at 3 and 4 weeks and a 4.5-fold increase at 5 weeks. Mature CCI OL showed a sharp loss at 2 and 4 weeks suggesting two cycles of cell death. Densitometry analysis showed ferritin labeling increased about 3 and 4-fold at 2 and 3 weeks, suggesting iron overload; a sharp loss at 4 weeks consistent with loss of OL, and a rapid increase at 5 weeks, which may reflect iron being utilized by newly formed OL for remyelination. These results suggest that disruption of iron homeostasis resulting in iron accumulation may lead to death of OL and OPCs in CZ induced demyelination.

1-C -93 The structural basis for Parkin-mediated mitochondrial quality control

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Mutations in the Parkin and PINK1 genes cause familial forms of Parkinson?s disease (PD). Parkin and PINK1 work together in mitochondrial quality control pathway essential to prevent neurodegeneration. The kinase PINK1 senses damaged mitochondria by accumulating at depolarized membranes and phosphorylating ubiquitin. Phospho-ubiquitin (pUb) then recruits and activates the E3 ubiquitin ligase Parkin. Parkin ubiquitinates outer mitochondrial membrane proteins, marking them for proteasomal degradation and recruiting the autophagy machinery. We along with others have previously shown that Parkin adopts an auto-inhibited conformation (Trempe et al. 2013). The release of inhibition is initiated by pUb binding to the RING1 domain of Parkin, which allosterically displaces its Ubl domain (Sauvé et al., 2015). This promotes phosphorylation of the Ubl at Ser65 by PINK1 and increases ubiquitin ligase activity. However, the molecular mechanisms underlying the conformational changes and substrate specificity on mitochondria remain unclear. Here, we dissect the steps of Parkin activation through a combination of biophysical measurements, mitochondrial ubiquitination and cellular mitophagy assays. Mutation of Trp403, which anchors the Repressor Element of Parkin, rescues the phospho-dead mutant S65A, supporting our hypothesis that S65 phosphorylation releases the REP and enables E2-binding. These rescue experiments pave the way for novel therapeutic approaches that could restore activity of impaired Parkin or PINK1.

1-C -94 Injury promotes the development of autoimmune peripheral neuropathy in predisposed inflammatory environment

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Autoimmune peripheral neuropathy has a serious consequence on patients' daily function and is sometimes life threatening. The etiology remains elusive but exposure to environmental factors such as viral/bacterial infection and injury is recognized to trigger disease. We demonstrated that co-stimulator factor B7.2 (CD86) transgenic mice L31 and L31/CD4KO develop spontaneous autoimmune peripheral neuropathy (APN) where massive infiltration of CD8 T cells and macrophages were found in diseased nerves. Here we further report that CD8 T cells in these mice have an effector/memory phenotype before disease onset, exhibiting CD44hiCD43+, CD44hiCD62-Llo, CD127loKLRG1+ expression pattern, which bears a resemblance to T cell inflation following persistent CMV infection in human and murine model. Strikingly, an injury to a peripheral nerve in L31 and L31/CD4KO mice accelerates the development of autoimmune neuropathy in other un-injured nerves. By disrupting blood nerve barrier, cross-presenting specific Ags from peripheral nerves and enhancing B7.2 expression on activated macrophages, injury can promote the development of APN. However, effector/memory CD8 T cells in the blood are required for disease initiation, since injury per se can never trigger autoimmune response in peripheral nerves of wild type mice. Thus, our findings revealed a decisive role of a predisposed post-infection-like immune background in the genesis of autoimmune response. It presents a new paradigm for understanding how coincidence of several environmental triggers can promote autoimmune diseases.

1-C -95 Pro and anti-inflammatory markers after experimental brain ischemia are different in microglia and infiltrating peripheral macrophages

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We studied the expression of pro- and anti-inflammatory markers after a permanent Middle Cerebral Artery Occlusion (pMCAO). LysM-EGFP knockin mouse were used to distinguish infiltrating macrophages (MΦ) from microglia (Mg) at the infarct. Immunostaining brains 3 days post-pMCAO with P2ry12 (a Mg marker), Iba-1, and EGFP confirmed that the P2ry12-, Iba-1 MΦ were EGFP , while P2ry12 , Iba-1 Mg did not express EGFP. The peak of EGFP myeloid cell infiltration was 72h post-ischemia and these cells were distributed evenly within the lesion core surrounded by a dense region of Mg. Flow cytometry analysis showed that a significantly higher percentage of Mg expressed TNF-α at 3 and 7 days post-pMCAO compared with infiltrating MΦ and by immunostaining we confirmed that Mg surrounding the lesion express TNF-α. Mg and MΦ were purified by FACS 72h post-ischemia to assess the mRNA expression of inflammatory markers. MΦ upregulated mRNA expression of arginase-1 (Arg-1) by 1000-fold, and IL-1β by 100-fold as compared to Mg. At the protein level, a significantly higher number of MΦ in the lesion core express Arg-1 while few if any Mg expressed Arg-1. However, IL-1β protein was not detected in MΦ by flow cytometry or immunofluorescence of tissue sections but was instead detected in astrocytes around the lesion. A PCR-array screening to further characterize the inflammatory gene profile revealed that MΦ showed upregulation while Mg showed down-regulation of many inflammatory genes in the ischemic brain. Our results show clear differences between Mg and MΦ 3 days after ischemic stroke.

1-C -96 Study of the effect of Polo-like kinase 2 on Alzheimer's disease related proteins and its implication in Alzheimer's disease

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Recent evidences support the role of Polo-like kinase 2 (PLK2) in Alzheimer's disease (AD) pathogenesis, notably the abnormal accumulation of PLK2 in AD-affected brains and the link between PLK2 polymorphism and AD risk. However, the exact mechanism by which PLK2 contributes to neuronal loss in AD remains elusive. OBJECTIVE : To identify the role of PLK2 in amyloid precursor protein (APP) and tau accumulation and its implication in AD pathogenesis. METHODS : Using immunohistological approach, we assessed the expression of PLK2 in APP-positive plaques and Tau-positive tangles in the brain of transgenic mouse models of AD. Then, the effect of PLK2 on APP and tau expression levels has been assessed in a cell-based assay (HEK-293). To modulated PLK2 activity, we used a combination of genetic and pharmacological approaches and assessed their impact on APP and tau expression levels. RESULTS : Using brain sections from 3xTG-AD transgenic mice, we report colocalisation of PLK2 and APP-positive plaques. In cell culture, we observed that PLK2 overexpression induces a reduction of APP protein levels and no effect has been observed on tau expression. These results were confirmed by the suppression of these effects after the genetic and pharmacological inhibition of PLK2 activity. CONCLUSION : Our results suggest that PLK2 activity modulates APP protein levels and may affect its accumulation in vivo. These data will help decorticating the role of PLK2 in AD pathogenesis and it will offer the opportunity to develop new pharmacological approaches for the treatment of AD.

1-C -97 Acting at a distance: cerebellar tumour mechanisms that disrupt neural stem cell function and cognitive development

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Long-term cognitive impairments are frequently observed in pediatric brain cancer survivors. While these impairments were initially thought to arise from irradiation and treatment, recent reports suggest a link to tumor-specific mechanisms. We therefore hypothesised that cerebellar tumors, more specifically medulloblastomas (MB), can directly perturb neural precursor cell (NPC) function and normal cognition by secreting bioactive factors. Cells derived from multiple MB patients were cultured, conditioned medium (CM) was collected and applied to embryonic (E13.5) cortical precursor (CP) and early postnatal (P7) subventricular zone (SVZ) NPC cultures. Treatment of CPs with CM acutely increased proliferation after 2 days and promoted gliogenic differentiation after 7 days. Treatment of P7 SVZ NPCs with CM increased proliferation both in monolayer cultures and neurosphere assay. To assess the effect of MB tumours on NSC function in vivo, we established MB subcutaneous flank xenografts in mice. Initial results reveal that after 30 days, mice with MB tumours had two-thirds fewer NPCs in the SVZ than control mice. Together, this suggests than tumors secrete factors that induce NSCs to prematurely and excessively differentiate resulting in the exhaustion of the NPC pool. Using transcriptomics and receptor proteomics, we have generated a tumor-NPC communications network that we have used to predict the ligands secreted by MB cells that can perturb NPC function. These data support the idea that brain cancers may have direct effects on NPCs, and we predict, cognitive function.

1-C -98 Macrophage activation profiles in spinal cord injury pain

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Infiltration of circulatory macrophages into the central nervous system (CNS) plays an important role in the pathobiology of spinal cord injury (SCI), including tissue damage and revascularization. Inflammatory mediators (e.g., cytokines/chemokines, proteases, and lipids) secreted by activated macrophages have been shown to modulate pain responses by acting directly/indirectly on ion channels and receptors expressed by the nervous system. However, little is known about the contribution of channels/receptors expressed by macrophages to the pathogenesis of pain in SCI. We therefore sought to identify channels/receptors that are upregulated by macrophages after SCI, and determine whether they may contribute to the development or maintenance of chronic SCI pain. We began by profiling the acute and chronic changes in pain behaviour following moderate contusion injury in female C57BL/6J mice and found significant changes in thermal (Hargreaves/acetone tests) and mechanical (von Frey test) hypersensitivity relative to sham-injured mice. We then identified ion channels and cell-surface receptors expressed by macrophages isolated from the spinal cord after SCI using Affymetrix GeneChip microarrays. An in vitro macrophage activation assay was performed to identify whether specific targets of interest were expressed after stimulation with LPS. Understanding and modulating macrophage phenotype by targeting expressed channels/receptors can lead to the identification of novel therapeutic targets that may help reduce pain after SCI, for which there are no viable treatments at this time.

1-C -99 Intra-nigral infusion of saporin-conjugated quantum dots promotes microglial activation and dopaminergic degeneration

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Microglia depletion systems have been used to delineate the relationship between neuroinflammation and neurodegeneration, but come with many limitations. To sidestep these limitations, we employed a relatively new biological assay centered around saporin-conjugated quantum dots. Saporin is a type I ribosomal inhibitor protein which, when conjugated to a delivery molecule, has been used to selectively destroy targeted cells. Quantum dots are fluorescent semiconductor nanocrystals which are selectively taken up by microglia via clatherin-mediated endocytosis and can be used in conjunction with saporin to make a microglia-specific toxin (QD-SAP). We utilized QD-SAP to target substantia nigra (SNc) microglia and consequently, affect dopamine neurons. To this extent, C57Bl6/n mice received a central infusion of QD-SAP into the SNc and were subject to Catwalk, Micromax, and Rotarod tests of motor functioning. Interestingly, QD-SAP did promote marked alterations in home-cage activity, along with deficits in motor coordination. These behavioral changes were paralleled by a robust activation of microglia and a reduction in dopaminergic neurons. These data may have important implications for Parkinson's disease and microglial-dependent mechanisms of neuronal degeneration.

1-C -100 Sox9 conditional knockout mice demonstrate improved recovery and increased reparative sprouting following middle cerebral artery occlusion

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Limited recovery from stroke has been attributed to structural and functional plasticity that compensate for lost functions due to damage. This plasticity is limited in part by the presence of growth inhibitors in the central nervous system. Preclinical studies using experimental models of stroke have shown that blocking or reducing signals from these inhibitors of axonal sprouting such as Nogo and chondroitin sulfate proteoglycans (CSPGs) increases post-stroke axonal sprouting and improves recovery. We identified the transcription factor SOX9 as a key up-regulator of CSPG production and demonstrated that conditional Sox9 ablation leads to increased axonal sprouting and improved recovery of hind limb

function after spinal cord injury. In the present study we evaluate the effect of conditional Sox9 ablation in a middle cerebral artery occlusion (MCAO) model of stroke. We demonstrate that conditional Sox9 ablation leads to reduced perilesional CSPG levels and of CSPG-rich perineuronal matrix at sites distant to the injury. These changes in CSPG levels is accompanied by improved post-stroke neurological recovery. We demonstrate that in the Sox9 conditional knockout mice corticorubral and corticospinal projections from the contralesional, uninjured cortex increase projections to targets in the midbrain and spinal cord denervated by the injury. These results suggest that neurological recovery in MCAO-injured Sox9 conditional knockout mice is improved due to a decreased levels of CSPGs that creates an environment that promotes reparative axonal sprouting.

1-C -101 Alteration of Striatal Synaptic Function by Tumour Necrosis Factor-alpha in Mice Model of Huntingtons Disease

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Huntington's disease (HD) is a neurodegenerative disease caused by an autosomal dominant mutation resulting from a variable expansion of a CAG repeat encoding polyglutamine. In this study, we used yeast artificial chromosome (YAC) mouse model of HD which expresses human huntington's gene containing 128 CAG repeats (YAC128). We have previously reported that TNF-α contributes to homeostatic plasticity and differentially regulates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor trafficking. Here we investigated whether TNF-α signaling is altering striatal synaptic function in medium spiny neurons (MSNs) in HD mice model. We performed whole-cell voltage clamp recording on MSNs in acute striatal slices from adult (8-10 week old) mice. The strength of cotico-striatal glutamatergic input was measured by targeting fluorescent dopamine D1 receptor expressing neurons and recording the ratio of AMPAR to N-methyl-D-aspartate receptors (NMDAR) mediated excitatory post-synaptic currents (EPSCs) both in WT and HD mice. We found that AMPA/NMDA ratio was significantly higher on D1-expressing MSNs from YAC128 mice vs WT littermates (n = 26). No change in AMPA/NMDA ratio was found in YAC128 on a TNF-α -/- background (n = 24) and was indistinguishable from TNF-α -/- alone (n = 25). There were no significant changes in AMPA/NMDA ratios in dopamine D2-expressing MSNs in any condition (n = 18). Collectively, our findings suggest that TNF-α regulates striatal synapses and alters glutamatergic inputs to MSNs thought to underlie many striatal dysfunctions.

1-C -102 A rapid chemical-genetic screen utilizing impaired movement phenotypes in C. elegans models of Autism Spectrum Disorder (ASD)

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Austism spectrum disorder (ASD) is the most common neurodevelopmental disorder with a constantly increasing prevalence. A promising way of identifying underlying cellular and molecular mechanisms of the disorder to develop novel therapeutic approaches is the usage of model organisms. A simple animal such as the nematode Caenorhabditis elegans is ideally suited to gain insights into the extreme complexity of ASD genetics. Despite its potential, using C. elegans in ASD research is a controversial approach and has not yet been done extensively. In this study, we present a screening of potential C. elegans mutants that can model for ASD. We screened these mutants for motor-deficiency phenotypes, which can be exploited to study underlying mechanisms of the disorder. Selected motor-deficient mutants were then used in a comprehensive drug screen, which comprises over 3600 FDA-approved and natural compounds that were analyzed for their ability to suppress motility defects caused by ASD mutations. This genetic-chemical approach, i.e. establishing C. elegans models for ASD and screening of

a well-characterized compound library, might be a promising first step to understand the mechanisms of how gene variations cause neuronal dysfunction, leading to ASD and other neurological disorders. Positively tested substances could also be promising candidates for clinical studies.

1-C -102 A rapid chemical-genetic screen utilizing impaired movement phenotypes in C. elegans models of Autism Spectrum Disorder (ASD)

Kathrin Schmeisser[1], Alex Parker[1]
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Austism spectrum disorder (ASD) is the most common neurodevelopmental disorder with a constantly increasing prevalence. A promising way of identifying underlying cellular and molecular mechanisms of the disorder to develop novel therapeutic approaches is the usage of model organisms. A simple animal such as the nematode Caenorhabditis elegans is ideally suited to gain insights into the extreme complexity of ASD genetics. Despite its potential, using C. elegans in ASD research is a controversial approach and has not yet been done extensively. In this study, we present a screening of potential C. elegans mutants that can model for ASD. We screened these mutants for motor-deficiency phenotypes, which can be exploited to study underlying mechanisms of the disorder. Selected motor-deficient mutants were then used in a comprehensive drug screen, which comprises over 3600 FDA-approved and natural compounds that were analyzed for their ability to suppress motility defects caused by ASD mutations. This genetic-chemical approach, i.e. establishing C. elegans models for ASD and screening of a well-characterized compound library, might be a promising first step to understand the mechanisms of how gene variations cause neuronal dysfunction, leading to ASD and other neurological disorders. Positively tested substances could also be promising candidates for clinical studies.

1-C -103 Structure and expression of the zebrafish ortholog of C9ORF72, with mutations in ALS.

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Amyotrophic lateral sclerosis (ALS) is a debilitating and fatal neurodegenerative disease that affects motor function. Limited therapeutic treatments exist for the disease that manifests clinically in adults and is characterized by the selective degeneration of lower and upper motoneurons. Recently, large GGGGCC repeat expansions were identified in the first intron of chromosome 9 open reading frame 72 (C9ORF72), an evolutionarily conserved gene whose function remain mostly unknown, in both familial and sporadic ALS and frontotemporal dementia cases. Zebrafish (ZF) models of knockdown/knockout and of transient overexpression of a gene orthologue of C9ORF72 have shown motor deficiency. The ZF is an excellent model to study neural development and pathology and its characterized cell biology and genome offer additional advantages for it as a model organism. The optical transparency of ZF embryos as well as the possibility to employ fluorescent markers in vivo offer additional advantages to this model. This project aims to elaborate the spatial and temporal profile of expression of each of the three predicted C9ORF72 transcripts in wild type ZF embryos fixed at varying stages of development. We are using quantitative PCR with specifics probes targeting each C9ORF72 transcript, and in situ hybridization with C9ORF72 specific digoxigenin labeled RNA probes followed by immunohistochemical observations. Characterizing the natural pattern of expression of C9ORF72 at varying stages of development in ZF shall assist in elucidating its function in fundamental cell biology.

1-C -104 Probing a Homeostatic Loop Linking the Fragile X Mental Retardation Protein and Methyl CpG Binding Protein 2

Jason Arsenault[1], David Hampson[2]

[1]University of Toronto, [2]Sick Kids and University of Toronto

Rett Syndrome, caused by a MECP2 gene mutation, and Fragile X Syndrome, caused by a FMR1 gene mutation, share overlapping autism-related endophenotypes. The mRNA coding for Methyl CpG binding protein 2 (MeCP2) has been identified as a substrate for the mRNA-binding protein Fragile X Mental Retardation Protein (FMRP). Here, we describe a homeostatic relationship between these two key regulators of gene expression. Brain levels of MeCP2 protein were significantly elevated in Fmr1 knockout (KO) mice compared to wild-type mice, and MeCP2 overexpression was normalized after a single intracerebroventricular injection of an adeno-associated viral vector coding for FMRP (AAV-Syn-FMRP). AAV-Syn-FMRP also alleviated the hyperactive locomotor phenotype in Fmr1 KO mice. Surprisingly, MeCP2 expression in the cerebral cortex correlated with the severity of the hyperactive phenotype. Single cell densitometric quantification of MeCP2 showed an inverse correlation with FMRP expression in the cortex of Fmr1 KO mice injected with AAV-Syn-FMRP. This finding was corroborated by flow cytometry experiments, where high FMRP expressing neurons displayed low MeCP2 levels, and vice-versa. Finally, MeCP2 KO mice displayed reduced FMRP expression, indicating that MeCP2 contributes to FMRP up-regulation. Together, these findings evoke a FMRP/MeCP2 regulatory mechanism that functions to balance the level of transcription and translation required for normal neuronal activity and could shed light on the sexual dimorphism of behaviour. This study was funded by the CIHR and the FXRFC.

1-C -105 Impact of spinal cord injury on tau pathology

Amy Bouchard[1], Franck Petry[1], Nicolas Josset[1], Françoise Morin[1], Yelena Boccacci[1], Maud Gratuze[1], Frédéric Bretzner[1], Emmanuel Planel[1]
[1]Université Laval

Tau is an axonal protein that stabilizes microtubules. In disease conditions, tau becomes hyperphosphorylated and forms aggregates in neurons. Tau pathology is present in various neurodegenerative diseases called tauopathies, which include Alzheimer's disease (AD) and traumatic brain injury (TBI). Patients with spinal cord injuries (SCI) have been found to develop long-term cognitive deficits like those with TBI. However, no study has examined the effects of SCI on tau pathology in the brain. Therefore, we hypothesized that SCI may induce tau pathology in both the spinal cord and brain, causing cognitive deficits. Our primary objectives consisted of evaluating the effects of SCI on tau pathology; understanding tau's mechanisms of hyperphosphorylation following SCI; examining the consequences of SCI on tau function. Transgenic hTau mice were used (which contain all six human tau isoforms, have no mouse tau, and develop tau pathology). SCI was induced by a hemi-lesion of the spinal cord and tau hyperphosphorylation was examined by Western blot analysis. Tau hyperphosphorylation was found at several epitopes in various brain areas, such as the right and left motor cortex, when compared to the sham and control groups. This study is the first to show tau hyperphosphorylation in the brain following SCI. Further studies will be necessary to determine whether brain tau pathology following SCI is the substrate for cognitive deficits.

1-C -106 Cerebellar Networks are altered in Autism - Examined with Mouse Models

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Background - Over the past 7 years, we have established a large cohort of mouse models related to autism. This allows for investigation of a large autism population in the mouse. The cerebellum has been frequently found to be different in autism and autism related disorders (see reviews by Tsai, 2016,

Hampson and Blatt 2015, and D'Mello and Stoodley 2015), so the question we asked was: Can we detect cerebellar differences across our model autistic population? Methods - The data used in this study was accumulated from 44 different autism mouse-lines and included greater than 60 genotypes and over 1500 mice. Using a 7.0T MRI to acquire high-resolution anatomical images of the brain and deformation based morphometry (Lerch et al. 2011); we measured volume differences in individual voxels and different cerebellar regions across the autism models. Results - The cerebellum as a whole was one of the most affected regions across the brain (Ellegood et al. 2015), and for this work, was further divided into 4 different subgroups, the cerebellar cortex, hemispheres, vermis, and deep cerebellar nuclei (DCN). Out of those regions only the DCN, the outputs of the cerebellum, were significantly smaller in the autism group (t-value of -4.26). Therefore, we further examined the projections from the DCN using anatomical covariance to assess the structural connectivity (Evans, 2013). The connectivity was altered only between the DCN and cortex. This alteration preferentially affects the somatosensory, visual and association corticies. Further investigation is warranted to determine the

1-C -107 Physical exercise impacts functional connectivity in pediatric brain tumour survivors

Sonya Bells[1], Elizabeth Cox[1], Diana Harasym[2], Samantha Gauvreau[1], Jovanka Skocic[1], Cynthia de Medeiros[1], Eric Bouffet[1], Colleen Dockstader[3], Donald Mabbott[1]
[1]The Hospital for Sick Children Research Institute, [2]McMaster University, [3]University of Toronto

Children treated for brain tumours exhibit impaired neural processing due to structural damage. Exercise induces structural repair mechanisms in both humans and rodents, and improves behavioral function following injury. It is unknown whether these benefits translate to neural communication evaluated by magnetoencephalography (MEG). We wish to investigate the functional connectivity changes related to exercise training in a group of children who were treated with cranial radiation for brain tumours. Exercise training involved 90-minute sessions of aerobic activity 3 times/week. To examine changes in neural communication, resting-state and a simple visual-motor reaction-time task were acquired using MEG (N=28). Within following networks: default, motor, dorsal attention, ventral attention, visual and cerebellum. data was filtered into delta (2-3Hz), theta (4-7 Hz), alpha (8-12Hz), beta (13-29Hz), low gamma (30-59Hz) and high gamma (60-100Hz). Phase lag index was compared between pre- and post-exercise in these networks. Following training, resting state analysis revealed increased high gamma connectivity in the dorsal attention network (p=0.049) and beta connectivity in the cerebellum network (p=0.029). Within the task-based analysis there was also a trend towards significant greater alpha connectivity in the cerebellum network (p=0.071). Overall, results suggest exercise enhances functional connectivity in dorsal attention and cerebellum networks. Thus, exercise may be an effective intervention to remediate cognitive deficits in children treated for brain tumours.

1-C -108 Small molecules that activate RET signals independent of GFR?Ñ1 co-receptors offer a novel therapeutic strategy for Retinitis Pigmentosa

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The growth factor Glial cell line-Derived Neurotrophic Factor (GDNF) binds to receptors RET and GFRa1, which are expressed throughout the nervous system. As GDNF receptors generate survival signals for neurons, GDNF has been proposed as a therapeutic to prevent or delay neuronal death in degenerative diseases, including Parkinson's, ALS, and eye diseases such as glaucoma and retinitis pigmentosa (RP), a blinding condition caused by a progressive loss of light-sensitive cells in the retina. However, despite continued efforts, GDNF has been unsuccessful clinically, owing to its poor distribution and instability.

Our lab is developing solutions to these issues through small molecules capable of mimicking GDNF pro-survival function. The newly discovered agents are being tested as therapeutics in mouse models of RP and other neurodegenerative conditions.

1-C -109 Aberrant ER Stress Response in Mouse Embryonic Fibroblasts Lacking the Sigma-1 Receptor

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

Endoplasmic Reticulum (ER) stress leads to the activation of the unfolded protein response (UPR), which aims to restore proteostasis. However, if ER stress is not mitigated, the UPR may trigger apoptosis. The Sigma-1 receptor (σ1R) is an ER resident protein thought to be involved in the UPR. Activation of the σ1R affords neuroprotection during ER stress, while σ1R "loss-of-function" mutations result in sustained ER stress and are linked to several neurodegenerative diseases including Amyotrophic Lateral Sclerosis (ALS). However, little is known about how the σ1R modulates the UPR in response to ER stress. To address this, we performed RT-PCR, Western Blot, and Luciferase experiments on Mouse Embryonic Fibroblasts (MEFs) isolated from either WT or σ1R−/− mice, and induced UPR activation using the ER stressor Tunicamycin (Tun). In baseline (unstressed) conditions, there was a significant increase in UPR activity in the σ1R−/− MEFs. As expected, WT MEFs exhibited robust activation of the UPR following induction of ER stress by Tun. However, the response to Tun was significantly attenuated in σ1R−/− MEFs compared with WT and survival during Tun treatment was comparable between the two cell types. Our data suggests that the σ1R modulates the initiation and intensity of the ER stress response. Sustained ER stress may be a mechanism by which motor neurons degenerate in diseases with σ1R mutations, such as ALS and distal hereditary motor neuropathies. Furthermore, understanding the role of the σ1R in ER stress may lead to novel treatments in other neurodegenerative disorders.

1-C -110 Treatment of AB-Variant GM2 Gangliosidoses Using Adeno-Associated Virus Serotype 9 in a Mouse Model

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[1]Queen's University, [2]University of North Carolina

GM2 gangliosidoses are a group of neurodegenerative diseases. GM2 ganglioside is normally degraded in a cell?s lysosomes through three gene products, HEXA, HEXB, and GM2. A defect in any one gene can result in a deficiency of Hexosaminidase A (HexA) enzyme activity toward GM2-ganglioside, which then cannot breakdown. The AB-variant is characterized by a mutation in the GM2A gene that encodes the GM2-activator protein, a required co-factor for the breakdown of GM2 gangliosides by the HexA protein. An effective viral vector known as Adeno-associated virus serotype 9 (AAV9) has previously been successful in pre-clinically treating the two other forms of GM2 gangliosidosis. The aim of this study is to give a one-time treatment of AAV9.GM2A viral vector therapy at a dose of 1 x 10^14 vector genomes per kilogram. Treatments were given intravenously to neonatal and adult mice. These mice undergo monthly behavioural testing, as well as biochemical and molecular analysis, performed at 20 and 60-week end-points. We hypothesize that an optimized AAV9.GM2A treatment can correct the gene deficiency and phenotype of the AB-variant in mice. Preliminary behavioural data show no statistical significance, which is expected since the phenotypic characteristics in the GM2A deficient mouse model develop after 20 weeks. Preliminary biochemical data for the short-term cohort showed a decrease in

GM2 gangliosides, however not significant, of the treated mice when compared to vehicle treated. This research will provide a step forward towards our goal of human clinical gene therapy trials.

1-C -111 Polygenic markers of resilience; a genome-wide approach

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[1]McGill University

Exposure to stressful events can cause differing sequelae depending on the level of stress resilience of each person. Here we studied resilience in the context of the development of substance dependency upon exposure to environmental insults. Data from the SAGE repository was split into testing and training subsets(n=1646 each). Subjects who were exposed to environmental insults were classified as resilient if they did not have a dependency and vice versa. We performed a genome-wide association study (GWAS) of resilience on the training subset(total number of SNPS:4599668). 59 SNPs passed a suggestive threshold ($p \leq 1e\text{-}5$). The smallest P-value for our study was observed with a marker on chromosome 3, rs709465 ($p=8.1e\text{-}7$,OR=-0.3). To identify novel associated genes, we ran a gene-based analysis using vegas on the unfiltered outcome of the GWAS. The top hit was DLEU1 ($p=9.9e\text{-}7$). We devised a polygenic propensity score (PPS) to facilitate the comprehensive quantification of the genetic propensity for resilience. A logistic regression modelled that, in the independent testing subset, the PPS was sufficient to predict resilience, ($p<2e\text{-}16$, pseudo $R^2= 0.57$). Based on the receiver operator curve analysis we calculated that the AUC was 0.94 (accuracy = 0.89). Together these show that our model can recapitulate(and quantify) the genetic underpinnings of resilience. This is one of the first GWAS to study the genetic architecture of environmental responsivity. Our proposed polygenic score of resilience has deep rooted clinical implications for drug prescription and intervention efforts.

1-C -112 Characterizations of vestibular and optokinetic reflexes in a mouse model of spinocerebellar ataxia type 6

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[1]McGill University

Spinocerebellar Ataxia Type 6 (SCA6) is a mid-life onset neurodegenerative disease that affects motor coordination. This autosomal dominant disease is caused by the expansion of a CAG repeat tract in a CACNA1A gene that encodes the α1A subunit of the P/Q type voltage-gated Ca2+ channel. A hyper-expanded polyglutamine (84Q) mouse model of SCA6 (SCA6 84Q/84Q), is characterized by impaired locomotive function. Using both in vitro and in vivo recordings, we have recently shown that the firing precision of cerebellar Purkinje cells in lobule 3 is significantly reduced in 7-month-old SCA6 84Q/84Q mice (Jayabal et al., 2016). A recent study has further demonstrated an impairment in eyeblink conditioning in a different, Purkinje-cell specific SCA6 mouse model, likely due to alteration in the cerebellar circuitry (Mark et al., 2015). Accordingly, we hypothesized that SCA6 84Q/84Q mice would likely show deficits in other cerebellar-dependent behaviors. To test this hypothesis, we characterized their vestibular-ocular reflex (VOR) and optokinetic reflex (OKR) by quantifying their eye movements. Our preliminary data shows that SCA6 mice displayed an approximately 20% reduction of both the VOR and OKR gain without a change in phase compared to litter-matched control WT mice. This result is consistent with altered neuronal responses processing within the floccular lobe of SCA6 84Q/84Q mice, suggesting the impairment of this region of the vestibular cerebellum that is known to play a vital role in the calibration of the VOR pathway as well as generation of the optokinetic responses.

1-C -113 Microglia-mediated effects of inflammation on visual system development in the zebrafish

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Neuroinflammation initiated by maternal infection during fetal development has been strongly implicated in the etiology of neurodevelopmental disorders, including epilepsy and schizophrenia. Preliminary results from our lab show that treatment of zebrafish larvae with bacterial lipopolysaccharide (LPS) to mimic infection causes arborization defects in retinal ganglion cell axons in vivo. Morpholino oligonucleotide knockdown of the PU.1 transcription factor to prevent differentiation of myeloid cells, including microglia, abrogates the effects of LPS, indicating a central role for microglia in this process. The pro-inflammatory cytokine IL-1β is both necessary and sufficient for the effects of LPS treatment. We have used Tg(Elav3:H2B-GCaMP6s) transgenic fish, in which the calcium indicator GCaMP6s is expressed pan-neuronally and targeted to the nuclei, to characterize neuronal responses to visual stimuli in the optic tectum of developing zebrafish larvae, with or without LPS exposure. Using resonance scanning and piezoelectric focusing, we performed high-speed in vivo 2-photon microscopy to image the calcium responses of hundreds of tectal neurons to visual stimuli and to measure the effect of LPS treatment on circuit activity. Understanding the mechanisms by which inflammation causes structural-functional dysregulation of developing neuronal circuits may provide insights to help mitigate or prevent neurodevelopmental and neuroinflammatory disorders. Funded by Molson Neuroengineering Fellowship (CMS), CIHR Vanier Award (NAIF), FRQS Research Chair (ESR).

1-C -114 NLRs as an endogenous inhibitor of inflammation in multiple sclerosis

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Objective Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that affects young people between the ages of 25-40. Inhibitors of immune response are the key targets for therapeutic intervention in MS. Previously, we reported protective roles of anti-inflammatory NLRs, Nlrp12 and Nlrx1, in the progression of experimental autoimmune encephalomyelitis (EAE). Here, we report the inhibitory role of Nlrx1 in predisposition to MS using a novel spontaneous (spEAE) and the classical MOG-induced EAE models. Methods To develop the spEAE, we generated myelin-specific TCR transgenic 2D2+Nlrx1-/- double transgenic mice. The disease progression was recorded and analyzed using a novel state-of-the-art behavioral system as well as clinical scores. We quantified the markers of inflammation in the spinal cords of spEAE mice using ELISA and immunofluorescence. T cell activation was evaluated using flow cytometry. Results Nlrx1-/- 2D2+ mice developed spEAE in 7-8 weeks of age, which resulted in complete paralysis of the hind limbs. There were significant increases in the expression of pro-inflammatory cytokines (TNFα and IL-1β), Iba1, and GFAP in the spinal cords of spEAE mice compared to littermate controls. Moreover, there was a significant increase in the percentage of CD4+ IL-9+ T cells in spleens of spEAE mice compared to WT controls. Conclusion This study demonstrates the protective role of Nlrx1 in MS. The spontaneous nature of EAE in double transgenic mice suggests that Nlrx1 suppresses tissue inflammation that is crucial for the development of MS.

1-C -115 High-throughput, in vivo drug screen identifies small molecules to rescue progranulin deficiency

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Progranulin (PGRN) is a widely-studied neurotrophic factor for its ability to reverse toxicity induced by amyloid β, TDP-43, and Huntingtin, and is an attractive therapeutic target for its role as a neuronal

survival factor. Mutations in the encoding gene result in either frontotemporal dementia (FTD) or neuronal ceroid lipofuscinosis (NCL). Despite the important role of this protein in the maintenance of neuronal health, there are no approved therapeutics capable of modulating the downstream molecular action of PGRN. Since performing large-scale chemical screens in vivo are costly and unfeasible in rodents, small model organisms are an attractive approach to address this issue. Caenorhabditis elegans is a nematode widely used for neuronal studies, and has been used to model human neurodegenerative disorders. Given its high homology with human genes, many genes are conserved, including PGRN with its ortholog PGRN-1. Initial characterization of C. elegans mutant worms null for pgrn-1 indicate they have motility defects leading to paralysis, so we used these phenotypes to carry out a high-throughput, whole-organism chemical screen. We screened ~4000 approved compounds for their ability to rescue pgrn-1(-)-induced phenotypes, and have translated our compounds into a zebrafish model of PGRN deficiency. We are currently validating our hits in a neuronal cell culture model. Given the multi-faceted role of PGRN, the successful hits from this screen will have potential applications outside the FTD and NCL fields.

1-C -116 MOTONEURON-SPECIFIC SILENCING OF THE SMN1 GENE IN ZEBRAFISH REPRODUCES HALLMARKS OF SPINAL MUSCULAR ATROPHY

Priyanka Jamadagni[1], Jean Giacomotto[2], Alexandra Lissouba[3], Kessen Patten[1]
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Spinal muscular atrophy (SMA) is an autosomal recessive motor neuron disorder caused by homozygous deletion or mutation of the SMN1 gene. It is the most common genetic causes of infant death and is characterized by characterized by lower motor neuron death leading to muscle weakness and atrophy. SMN1 is ubiquitously expressed, however, it is currently unclear how reduced SMN1 levels cause specific loss of motor neurons. Using a stable miR-mediated knockdown technology in zebrafish, we developed a system allowing transgenic spatio-temporal control of the smn1 gene. Motoneuron-specific silencing of smn1 is sufficient to reproduce SMA hallmarks, including abnormal motor neuron development, poor motor function and premature death. Interestingly, smn1 knockdown in motor neurons also induced severe late-onset phenotypes including poor motility, scoliosis-like body deformities, weight loss and muscle atrophy. The morphology of the neuromuscular junctions in these fish are currently being evaluated. Taken together, we have developed a new transgenic system allowing tissue-specific control of the smn1 expression in zebrafish. We found that smn1 silencing in motor neurons alone is enough to reproduce SMA hallmarks in zebrafish. Using this new model, we will now be able to further our understanding of SMA pathogenesis and more importantly identify therapeutic compounds through phenotypic screening.

1-C -117 Role of serotonin transporter gene in insomnia

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Insomnia is the most prevalent sleep disorder, affecting 4.5 million Canadians. Studies showed that insomnia is heritable yet little is known about contributing genetic factors. Insomnia is highly comorbid, especially to depression and anxiety. Similar pathophysiology between the three disorders is emphasized by the use of common pharmaceutical treatments targeting serotonergic pathway. Studies that aimed to identify genetic risk factors of insomnia have two major limitations: the use of small samples and the variability in measuring insomnia. Hence our objective is to follow a candidate gene approach to identify serotonin genetic factors of insomnia that have previously been associated with

depression and anxiety disorders. We hypothesize that severe cases of insomnia will be more strongly associated with genetic variation related to anxiety and depression compared to those who have mild insomnia. The cohort is composed of 675 insomnia patients diagnosed with primary insomnia and was advised pharmaceutical or psychotherapeutic treatments. The sample is stratified based on insomnia severity as reported by the insomnia severity index or by medical notes.

1-C -118 Diabetes Impairs the Microglial Response to Cerebral Microbleeds

Stephanie Taylor[1], Emily White[1], Craig Brown[1]
[1]University of Victoria

Diabetes is associated with cerebrovascular pathology such as microbleeds, stroke and impairments in cognitive function. The presence and burden of microbleeds in the brain has been strongly linked with cognitive decline and increased risk of dementia. Microglia, the resident immune cells of the CNS, are thought to play an important role in vascular repair since inhibiting these responses can exacerbate injury. Here, we hypothesized that diabetes, especially if not well controlled with insulin, will impair microglia responses to cerebral micro-bleeds and repair of damaged vessels. Using in vivo two-photon imaging, we show that chronic hyperglycemia in the streptozotocin model of type one diabetes leads to decreased microglial process accumulation around the site of microvascular injury without altering the general motility of these processes. Reduced microglial process accumulation around the microbleed was associated with increased permeability of fluorescent dyes from the damaged vessel 30 minutes after induction of the bleed. Importantly, this abnormal microglial response and vascular permeability could be partially prevented with tight control of blood glucose levels with insulin. Current experiments are underway to determine if suppressing inflammation in diabetic mice can restore normal microglial reactivity to cerebral microbleed. These results demonstrate that chronic hyperglycemia disrupts microglial based repair of damaged microvessels, which may help explain why diabetes is associated with greater a risk of cerebrovascular dysfunction and cognitive decline.

1-C -119 Mapping and manipulating the fate of obstructed microvessels

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Cerebral microvessels are prone to spontaneous obstructions which could have a major impact on cerebral circulation and brain function. However, what ultimately happens to these microvessels is unknown. Here, we used 2 photon imaging in Tie2-endothelial GFP mice to track the cerebral microvascular response to either natural obstructions or those artificially induced with 4 µm fluorescent microspheres. In healthy mice, most occlusions were resolved in 12 hrs, yet some were persistent, lasting for days. Those with prolonged occlusions either eventually recanalized or were pruned in a retraction reminiscent of reverse-angiogenesis. Of note, vessels never sprouted new branches to compensate for the obstruction or loss of a vessel. A small portion of vessels also recanalized by expelling the emboli through the vascular wall, something previously found only in larger vessels (Angiophagy). Surprisingly many vessels that cleared an obstruction and restored flow, still underwent retraction at a later time point, implying that recanalization does not ensure the long-term survival of a microvessel. Functionally, vessel pruning invariably increased blood flow/flux in adjacent microvessels. Using parallel strategies of pharmacological inhibition or inducible genetic knock down, we found VEGF-R2 signalling was a critical component of recanalization. These results provide new understanding of how microvascular obstructions, which regularly occur in the brain, could lead to progressive changes in the architecture and function of cerebrovascular networks.

1-C -120 Perampenel, an alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor antagonist inhibits glutamate cytotoxicity and reverses symptoms in a rat model of Status Epilepticus.

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Background: Status epilepticus (SE), a prolonged self-sustaining seizure is associated with high mortality and morbidity. Persistent activation of Ionotropic glutamate receptors contributes to seizure sustenance and neuronal cell death. This study assessed the efficacy of perampanel, an AMPA receptor antagonist, both in vitro and in vivo model of SE. Methods: Primary hippocampal cultures were prepared from E18 Sprague Dawley rats. Excitotoxicity was induced and the degree of neuronal cell death was determined by measurement of reduction product of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium (MTT), production level of Lactate Dehydrogenase enzyme (LDH), and the number of condensed nucleus using Hoechst staining. Using western blot and ELISA techniques, caspase-3 dependent apoptotic pathway was confirmed. The efficacy of Perampanel in a pilocarpine SE rat model was assessed. Spatial memory was tested using Y maze test. Hippocampal cell death was assessed by Fluoro-jade C staining. Results: Pretreatment with Perampanel reversed cell death in in-vitro experimental conditions. Compared to controls, SE rats showed deficit in performing Y maze, consistence with increased hippocampal cell death.Perampanel treatment terminated the seizure (based on EEG recording and behaviors related to epilepsy), and partially reversed these cognitive abnormalities and neurodegeneration in hippocampus. Conclusion: As effective intervention to terminate seizure is important to reduce the mortality of SE, our study provided the evidence that Perampanel could be an optional treatment in SE.

1-C -121 Hyperthermia induces tau dephosphorylation in vitro and in vivo

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Tau is an axonal protein whose main function is to associate with microtubules and stabilize the cytoskeleton. This function is regulated in part by phosphorylation. In pathological conditions, as in Alzheimer's disease (AD), tau becomes hyperphosphorylated and aggregates in neurons. To date, causes of tau disease during aging and AD are still unknown, but deregulation of thermogenesis may be one of the factors. Indeed, the elderly often have impaired thermoregulation and a body temperature somewhat lower than normal. In mice, we have previously demonstrated that even a small decrease in body temperature causes a significant hyperphosphorylation of the tau protein. Although the effects of hypothermia on the phosphorylation of tau are well documented, little is known about the effects of hyperthermia on tau. Our hypothesis is that hyperthermia may, contrary to hypothermia, cause a decrease in the phosphorylation of tau. To test this hypothesis, we used cell lines exposed at different temperatures ranging from 37 to 42 degrees celcius. We also exposed normal mice and mice models of tau pathology to a higher temperature. Our preliminary results demonstrate that hyperthermia causes rapid dephosphorylation of Tau protein both in vitro and in vivo. These results are very promising since this is the first time that tau protein can be dephosphorylated so extensively. These data could be a new avenue for the treatment of certain tau pathologies including Alzheimer's disease.

1-C -122 Plasmatic variations of Klotho, apolipoproteins J and D levels and the antioxidant capacity are correlated with cognitive decline in patients with Alzheimer´s disease and mild cognitive impairment

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Oxidative stress plays an early role in Alzheimer´s disease (AD). Oxidative damages were found to be elevated in the brain from mild cognitive impairment (MCI) and in AD patients. Some oxidative markers were also raised in plasma. However, their association with the progression of the cognitive decline remains to be determined. Objectives: To establish a specific pattern of redox biomarkers in plasma from MCI and AD patients and its correlation with two cognitive clinical tests. Methods: In plasma from patients with MCI and AD at different stages and from age-matched controls, we have measured the antioxidant capacity by electrochemical detection, Klotho by ELISA, protein carbonyls, apolipoprotein D and J (ApoD and J) by Western Blot. Results: An early decrease of the antioxidant capacity is observed from the MCI stage while Klotho and ApoJ levels increased from MCI group. Protein carbonyl levels were progressively increased from mild AD patients. Interestingly, the antioxidant capacity is correlated with both clinical scores MoCa and MMSE tests. Additionally, the protein carbonyls levels are correlated with the MoCA scores only. Conclusions: Our results indicate that the antioxidant capacity decreases with the progression of AD while oxidative damages increase in plasma. Interestingly, these peripheral oxidative markers are correlated with cognitive decline. Thus, peripheral specific oxidative pattern has a potential as blood-based biomarkers for MCI, AD and its progression. Supports: Chaire Louise & André Charron pour la maladie d´Alzheimer, Fondation INRS-IAF, INAF.

1-C -123 Braak neurofibrillary tangle staging prediction in Alzheimer's disease using in vivo MRI metrics

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Objective: To predict neurofibrillary degeneration associated with Alzheimer's disease (AD) from MRI measurements. Method: Participants were selected from three databases (ADNI, NACC, RUSH) providing MRI and pathological data. After quality control, 194 subjects were retained. Surfaces, thicknesses and volumes from bilateral structures were segmented from last MRI before death using FreeSurfer and transformed to normed metrics adjusted for sex, age, intracranial volume, manufacturer and magnetic field. Nonparametric analyses were performed to provide a predictive model of neurofibrillary staging as assessed by Braak score. Results: Amongst all 234 MRI variables, 16 measures from temporal structures (amygdala, hippocampus, inferior lateral ventricle, inferior temporal, entorhinal, perirhinal, fusiform and parahippocampal cortices) and one occipital structure (lateral occipital cortex) were significantly correlated with Braak stage (p=.005 significance threshold). We used these variables to build a predictive model using backward stepwise ordinal regression and 10-fold cross-validation. The best model included age at death and the normed scores of the left lateral occipital surface, and the left inferior lateral ventricle, right fusiform gyrus and right entorhinal cortex volumes, with an accuracy of 57.7% for the prediction of transentorhinal (I-II), limbic (III-IV) and isocortical (V-VI) stages. Conclusion: Regional atrophy reflects underlying neurofibrillary degeneration. MRI metrics may therefore be an avenue for prediction of AD pathological staging in the living brain.

1-C -124 Sensory Filtering and Social Behaviour in a Prenatal Immune Activation Model of Autism Spectrum Disorder

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Altered brain development is associated with neuropsychiatric disorders like Autism Spectrum Disorder (ASD) and schizophrenia. Epidemiological studies show that maternal infection during pregnancy increases the offspring's risk of developing these disorders, pointing towards maternal infection and the maternal immune response as causes of abnormal neurodevelopment. To model pathogen-free maternal immune activation, the viral marker Polyinosinic:polycytidylic acid (Poly I:C) is used to elicit an immune reaction. When injected in pregnant rodents, it has previously been shown to produce offspring with structural and behavioral changes relevant to ASD and schizophrenia. We investigated the effect of poly I:C-induced immune activation during mid-gestation in rats (Gestation Day 14) on two ASD domains, sensory filtering and social behavior. In adolescent rats, we found that GD-14 immune activation impaired visual but not auditory prepulse inhibition (PPI) of the acoustic startle response. In contrast, short and long-term habituation of startle were unaffected. In a social behavior test quantified by voluntary interaction time with a familiar rat compared with either an empty chamber (sociability) or an age-matched stranger (social novelty), adolescent GD-14 poly I:C offspring showed decreased sociability but normal social novelty. Visual sensory filtering and sociability impairments are relevant to ASD phenotypes and future studies will attempt to delineate how they change in adulthood and whether they correlate with anatomical and molecular changes.

1-C -125 Assessing the progression of early Alzheimer Disease (AD) and the role of intraneuronal amyloid beta and oxidative stress

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Background: Alzheimer disease (AD) remains to be the leading cause of dementia and there is a minimal understanding of the earliest, pre-symptomatic stages of AD. Since these stages are elusive, it is impossible to study them comprehensively in humans. Transgenic animal models provide the opportunity to elucidate these early, 'silent' stages which can signal suitable, early, therapeutic windows. Rationale: This project aims to understand the earliest, disease initiating molecular events of AD and the specific roles of intraneuronal amyloid beta and oxidative stress during this process. We hypothesize that intraneuronal amyloid beta accumulation initiates a pathological cascade, leading to oxidative stress that culminates in the classical AD pathology. Oxidative stress has been observed in late stages of AD but the role it plays in pre-symptomatic stages remains unknown. Approach: The McGill-R-Thy1-APP transgenic (Tg) rat model of AD (Cuello lab) will allow for studying the earliest stages of AD that are impossible at present to comprehensively study in humans. To address our aim, we have been developing methodologies for assessing oxidative stress in the Tg rat model by using novel fluorescent probes (Cosa lab) that specifically detect lipid peroxidation. Our preliminary results in isolated mitochondria, and acute hippocampal slices suggests that these approaches should provide insight into how intraneuronal amyloid beta and lipid peroxidation participates in the initiation of the AD pathology.

1-C -126 Hyperactive CDK5 Inhibitory Peptides - TP5 and Peptide A - Display Neuroprotective and Restorative Roles in the 6-OHDA Lesioned Model of Parkinson?s Disease

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Cyclin-dependent kinase 5 (CDK5) is a multifunctional enzyme involved in many neuronal development, maturation and survival functions. CDK5 activity is tightly regulated by its association with neuronal proteins p35 and p39. Upon neuronal insults, increased intracellular calcium activates calpain. This enzyme cleaves p35 to p25, which has a higher affinity for CDK5. Dysregulated CDK5 (CDK5/p25) then becomes hyperactivated and toxic to the cell. Thus, CDK5 hyperactivity initiates apoptotic cascades

leading to significant dopaminergic neuron loss, and has a destructive role in neurodegenerative disorders, such as PD. This study investigates the selective inhibition of CDK5/p25 by two novel peptides and their potential therapeutic role in PD. The first is TP5, a 24-amino acid peptide derived from p25/p35, and second is Peptide A, an 8-amino acid peptide derived from TP5. Neuroprotective and restorative effects of TP5 and Peptide A were tested using amphetamine-induced rotations (AIR) and footprint analysis (FP) in the unilateral 6-hydroxydopamine (6-OHDA) lesion model of PD. Results showed TP5 and Peptide A significantly attenuated AIR in lesioned rats, indicative of a neuroprotective role. FP measures gait impairments and exhibited significantly increased stride lengths in TP5 treated rats compared to controls, implying restorative effects of TP5. The neuroprotective and restorative results found using these peptides supports selective inhibition of CDK5/p25 and provides a framework for the development of novel therapeutics for the treatment of PD. Supported by NSERC, Canada.

1-C -127 Blocking Alzheimer's-associated phosphorylation at AT8, AT8/AT100 or S422 sites on tau does not affect tau-induced BDNF down-regulation in vitro

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Tau protein is abnormally hyperphosphorylated in the Alzheimer's disease (AD) brain, leading to the formation of toxic, soluble aggregates. Toxic tau reduces brain-derived neurotrophic factor (BDNF), a protein that is critical for neuronal function, plasticity and learning and memory. Hyperphosphorylation at certain sites on tau and down-regulation of BDNF are early events in AD pathology. Identifying which of these tau phosphosites are involved in BDNF down-regulation is the focus of this work. We hypothesize that, by inhibiting tau phosphorylation at key sites implicated in AD, we will block tau-induced BDNF down-regulation. We have stably transfected human neuroblastoma SH-SY5Y cells with the plasmid coding for wild-type human 4-repeat tau (htau40) and with htau40 carrying mutations of the phospho-epitopes AT8 (S202A/T205A), AT8/AT100 (S202A/T205A & T212A/S214A) and S422A. These mutations prevent phosphorylation at these epitopes, and at the S422A site blocks subsequent tau aggregation and truncation. Cells were differentiated and BDNF was quantified using real-time qRT-PCR and Western blotting. BDNF levels were down-regulated in SH-SY5Y cells stably transfected with tau mutated at all sites mentioned above. Therefore, BDNF down-regulation may not involve phosphorylation at these sites. Alternatively, BDNF down-regulation may depend on the phosphorylation and interplay of multiple tau sites, or tau over-expression alone, regardless of its phosphosphorylation state, may down-regulate BDNF. Further experiments will be carried out to investigate these possibilities.

1-C -128 Optimizing stimulation parameters and treatment fields for Intratumoral Modulation Therapy

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Introduction: The introduction of electrotherapy presents a pivotal advance in the treatment of the aggressive brain cancer, glioblastoma (GBM). Our group has been pioneering a novel electrotherapy termed Intratumoral Modulation Therapy (IMT), which delivers non-ablative current directly within GBM tumors. The goal of this study was to characterize the anti-tumor impact and predicted treatment fields using range of IMT parameters. Methods: Patient-derived GBM cells were treated with IMT using various stimulation frequencies, amplitudes and waveforms expected to be non-injurious to the normal brain. Cell viability was assessed via activated caspase-3 labeling, MTT spectrophotometry and flow

cytometry detection of cell death and apoptotic markers. Computer modelling using COMSOL was performed to predict spatial distribution of electric field strengths. Results: Tumor-selective, caspase-dependent apoptosis, with >30% reduction in GBM viability was consistently measured with MTT and flow cytometry in all permutations of IMT tested compared to sham conditions. Computer modelling corroborated with the level of tumor reduction observed and revealed specific technical limitations of the present electrode constructs. Conclusion: This proof-of-concept study demonstrates the potential of IMT as a putative new electrotherapy in the treatment of GBM. Advances in field prediction mapping will guide design of improved IMT hardware and stimulation parameters to optimize anti-GBM efficacy in preclinical models and, with success, clinical applications of IMT.

1-C -130 Impaired hypothalamic insulin signaling and peripheral metabolic dysregulation in AD animal models

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Clinical and epidemiological data shows that Alzheimer`s Disease (AD) is related to diabetes. AD patients have a higher risk of developing T2D and/or impaired glucose metabolism. Amyloid Beta Oligomers (ABOs), toxins that build up in AD patients brains, are known to induce ER stress and impair insulin signaling in the hippocampus of mice. In the current study we aim to investigate whether ABOs can also impact the hypothalamus, a region key for metabolic control, and trigger peripheral metabolic deregulation. WT mice and macaques intracerebroventricular (icv) injected with ABOs were evaluated. We further used transgenic mice models of AD (APPPS1 and CRND8) in this study. Glucose Tolerance Test (GTT) and Insulin Tolerance Test (ITT) were performed to access glucose homeostasis. Plasma insulin was measured by Elisa. Proteins related to insulin pathway were quantified by Western Blotting and markers of inflammation (IBA-1 and GFAP) were analyzed by Immunohistochemistry. Our results show that AβOs trigger hypothalamic inflammation and impaired insulin signaling leading to glucose intolerance and insulin resistance. In the transgenic mice models we identified glucose intolerance, but not insulin resistance. These results provide evidences of hypothalamic dysfunction in AD models and suggest impaired hypothalamic insulin signaling as a novel shared molecular mechanism between AD and T2D.

1-C -131 Early Parkinson Disease Progression: The Role of Intrinsic Brain Networks

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The network spread hypothesis postulates that neurodegeneration results from toxic aggregates of misfolded proteins that propagate along brain networks. Using baseline and one-year follow-up MRI from the large longitudinal dataset, we test if disease progression at baseline is best explained by spread along the brain's connectome from a subcortical "disease reservoir" measured at a one-year follow-up. Local cortical thickness was measured from T1-weighted 3T MRI scans of de novo Parkinson's Disease (PD) (n=105) and healthy controls (n=57). Cortical thickness changes were calculated by subtracting the values at one-year follow-up from baseline. Differences in change between PD and controls were analyzed. Disease exposure at each of the 463 cortical node (i) was defined as the functional or structural connectivity between that cortical node (i) and a subcortical area (j) multiplied by the atrophy of the subcortical area (j) calculated with deformation based morphometry at baseline. Using a resting

state fMRI-derived connectome, significant correlation was observed between whole-brain regional cortical thinning and disease exposure. Using a diffusion-weighted MRI structural connectome, cortical thinning and disease exposure were not significant at the whole-brain level but were significantly correlated within each hemisphere independently. Conclusions: Cortical changes in PD occur considerably earlier than previously reported. The pattern of cortical thinning is consistent with spreading from a subcortical disease reservoir to cortical regions via intrinsic brain networks.

1-C -132 Glutamine synthetase in endothelial cells of the blood-brain barrier: protecting the brain in hepatic encephalopathy?

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Introduction: Hepatic encephalopathy (HE) is a neuropsychiatric disorder which develops as a major complication of liver disease. Hyperammonemia is believed to play a major role in the pathogenesis of HE as ammonia easily crosses the blood brain barrier (BBB) causing toxicity. Glutamine synthetase (GS), an enzyme which removes ammonia, plays an important compensatory role in liver disease and has been found in muscle and brain (astrocytes). However, its expression in endothelial cells (EC) of the BBB has never been explored. Methods: GS protein and activity was assessed in 1) rat brain microvascular EC (+/- ammonia and conditioned media from chronic liver disease (CLD)) and 2) isolated cerebral microvessels (CMV) from naïve rats. Results: GS was co-localized with EC in brain of naïve rats. GS protein was detected in CMV, similar to that of brain but activity was less ($p<0.05$). In vitro, EC expressed GS protein and activity, but lower than brain ($p<0.05$). EC exposed to ammonia resulted in increased GS activity ($p<0.05$). However, ECs exposed to plasma from CLD rats had lower GS activity and protein compared to controls ($p<0.05$). Conclusion: We demonstrate for the first time that GS is present in EC and that GS activity is stimulated by ammonia but reduced conditioned plasma from CLD rats. This suggests other factors such as oxidative stress (present in CLD) could lead to GS inhibition. We speculate that a downregulation of GS in the BBB allows for a faster entry of ammonia into the brain and that upregulating GS in EC of the BBB could become a new therapeutic target for HE.

1-C -133 The Role of Stress-Inducible protein 1 (STI1) in cellular resilience and Alzheimer's disease

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Stress-inducible protein 1 (STI1) is a cochaperone for Hsp70/Hsp90 chaperone machinery and signals via cellular Prion protein (PrPC). Deletion of STI1 in mice is lethal and STI1 haplo-sufficient neurons are less resistant to insult by oxidative stress and β-amyloid oligomers (AβO). AβO, a major toxin in Alzheimer's disease (AD), bind to PrPC causing neuronal toxicity, which can be attenuated with extracellular STI1 treatment, or overexpression of STI1. We generated several mouse lines targeting STI1, including an overexpressing mouse line (TgA) and a line with hypomorphic alleles (dTPR1), lacking exons 1 and 2. We crossed these lines with the 5XFAD (FAD) mouse model of familial AD, overexpressing mutant Amyloid precursor protein. We used biochemical and cell biology assays to characterize these lines and investigated hippocampal amyloidosis and neurodegeneration with immunostaining. Contrary to our original hypothesis, TgAFAD mice presented faster and increased amyloidosis. Immunostaining results suggest accumulation of extracellular STI1 around plaques of TgAFAD mice. dTPR1 mice have 75% less mutated STI1 protein and show significant reduction in levels of several STI1-Hsp90 clients, including

tau, but increased cleaved TDP-43 levels. Our preliminary results indicate a complex role for STI1 in cellular resilience and reveals a novel role for Hsp90/STI1 chaperone machinery in amyloidosis. The mouse lines we generated will be critical to understand physiological and pathological roles of the Hsp70/Hsp90 chaperone machinery in several models of protein misfolding disease.

1-C -134 Expression of Cerebral Dopaminergic Neurotrophic Factor in Human Patients with Stroke and Dementia

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Cerebral dopamine neurotrophic factor (CDNF) is a protein which plays a critical role in protecting and repairing dopaminergic neurons. CDNF has been shown to have neuroprotective effects in many cellular and animal models. Despite extensive research, the ways in which the pathophysiology of neurological disorders affect the endogenous levels of CDNF expression remain unknown. Although early diagnosis of neurological disorders is difficult, it has the potential to improve treatment. In this study we examine CDNF mRNA expression in blood components of patients with stroke, dementia, Parkinson's Disease (PD), and healthy aged-matched controls in order to test its potential as a biomarker. Blood is an ideal candidate for the development of a biomarker as it is readily available in large quantities and it can be obtained through minimally invasive techniques. Blood has long been used to model serotonergic and dopaminergic neuronal behaviour and platelets exhibit biochemical impairments similar to the substantia nigra in patients with PD. CDNF mRNA expression has been shown to significantly decrease in platelets of patients with stroke and dementia compared to controls. This work was supported by CIHR.

1-C -135 Repeated Mild Traumatic Brain Injury: Insights from a new animal model.

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Mild traumatic brain injury (mTBI), and repeated mTBI, are becoming recognized by practitioners and the general public alike as significant global health concerns, however animal models have struggled to provide insight into the pathophysiology associated with the gradual progression of associated neurodegenerative syndromes. In particular, there is a paucity of research into how repeated mTBI affects the structure and function of the still developing paediatric brain. To address this issue we have developed an animal model that allows closed-head injuries to be produced in awake juvenile rats. Here we show that we can reliably produce both single, and repeated, awake closed head injuries (ACHI) in juvenile rats without producing skull fractures or inducing significant mortality. The ACHI model produces acute deficits that can be accurately quantified using a modified Neurological Assessment Severity Score (NASS) and that normally resolve in 24 hours. MRI found no evidence of overt brain damage or volumetric loss in the cortex, hippocampus, or corpus callosum. Despite the lack of morphological changes there were significant change sin both synaptic plasticity and anxiety-like behaviors in these animals. Our initial findings suggest that it may be a promising new platform upon which to base investigation into pediatric mTBI pathophysiology.

1-C -136 Anatomical correlates of functional recovery after treatment with metformin in a mouse model of cerebral palsy

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It has been shown that treatment with metformin results in activation of neural precursor cells and leads to functional recovery in a mouse model of cerebral palsy (Dadwal et al, 2015). The goal of the present study was to use whole brain, high resolution (40µm-iso), contrast-enhanced structural MRI (Nieman et al, 2006) to further characterize anatomical underpinnings of this previously observed behavioural recovery. MRI results were next used to guide tissue staining. The Vannucci hypoxia/ischemia (H/I) model of cerebral palsy was used. Briefly, neonatal mice (P8) were subjected to ischemic injury via ligation of the left common carotid artery and 1h hypoxia. Metformin was delivered to the pups from P9 to P15 through the milk of lactating mothers implanted with metformin releasing mini-osmotic pumps. Differences in brain anatomy between control mice (n=9), mice that were given metformin without H/I injury (n=8), mice with H/I injury only (n=9) and mice with H/I injury that were given metformin (n=10) were evaluated ex vivo at P23. In addition to an expected reduction in volume in the injured hemisphere (left), relative, regional volume increases in the contralateral hemisphere (right) were observed in all mice with the H/I injury. These increases were much more pronounced in mice treated with metformin in the area within the somatosensory cortex contralateral to the injury site. Tissue staining analysis are ongoing identify cellular underpinnings of the observed volume increases.

1-C -137 Focused ultrasound-mediated long-term delivery of a therapeutic in a mouse model of Alzheimer's disease

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Alzheimer's disease (AD) is characterized by deposition of amyloid-beta peptides (Abeta) in the brain. Therapeutics have been designed to target Abeta and reduce the associated pathologies. Anti-Abeta antibodies have entered clinical trials but have not significantly improved cognitive function. This limited success could be related to low bioavailability of antibodies due to the blood-brain barrier (BBB). Consequently, long-treatments using high dosages are required for intravenously administration. Using gene therapy, we transduced cells in targeted brain regions to mediate long-term production of an anti-Abeta therapeutic. We hypothesized that this long-term supply of therapeutic produced directly in the brain will counter amyloid pathology and improve cognitive function. The therapeutic was constructed and tested in vitro for binding affinity to toxic Abeta. The construct was delivered using a vector in a mouse model of AD, to the cortex and hippocampus using MRI-guided focused ultrasound, a non-surgical method of localized delivery to the brain. Long-term expression of the therapeutic was observed at 8 weeks and 20 weeks following delivery. Reduction of amyloid pathology at 8 weeks post-treatment was measured. Analyses of changes in pathology and cognitive behavior 14-20 weeks post-treatment are ongoing. In conclusion, we have developed a therapeutic with high affinity to toxic Abeta and a method that provides a non-surgical approach to deliver therapeutic constructs to brain cells, rendering them capable of producing a therapeutic factor for extended periods of time.

1-C -138 Rescue of ATXN3 Neuronal Toxicity in C. elegans by Chemical Modification of ER Stress

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Polyglutamine expansion diseases are a class of dominantly inherited neurodegenerative disorders that develop when a CAG repeat in the causative genes is unstably expanded above a certain threshold. The

most common dominantly inherited spinocerebellar ataxia caused by this expansion is the type 3 (SCA3), also known as Machado-Joseph disease (MJD). The gene causing MJD is ATXN3. The prevalence of MJD is increasing and there are no pharmacological therapies available that successfully treat this disease. Therefore, the development of novel therapeutics for MJD is urgently needed. In this study, we generated transgenic C. elegans strains expressing wild type or mutant human ATXN3 genes and tested them for recovery of motility defects, decreased lifespan, and neurodegeneration phenotypes upon treatment with compounds known to modulate ER stress and having neuroprotective roles. We observed differences between both transgenic lines and found that the motility defects, the reduced lifespan and neurodegeneration were rescued by compounds that have been previously identified in our laboratory. These compounds were also able to prevent the oxidative stress and the ER stress response induced by mutant ATXN3 in transgenic worms. We introduce novel C. elegans models for MJD based on the expression of full-length ATXN3 in GABAergic motor neurons. Using these models we discovered that chemical modulation of the ER unfolded protei response reduced neurodegeneration and could be a new therapeutic approach for the treatment of MJD.

D – Sensory and Motor Systems

1-D -139 Insulin signalling enhances AMPK activity, mitochondrial function and neurite outgrowth in adult sensory neurons

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Depressed mitochondrial function has been proposed as a key mediator of peripheral neuropathy. There is down-regulation of AMPK (master regulator of cell bioenergetics), mitochondrial gene expression and function in dorsal root ganglia (DRG) in animal models of type 1 and type 2 diabetes. We hypothesized that loss of direct insulin signaling in diabetes contributes to loss of AMPK activity and mitochondrial function in DRG neurons leading to development of sensory neuropathy. Adult DRG neurons were cultured from age-matched control or streptozotocin (STZ)-induced type 1 diabetic rats. Neurons treated with/without insulin underwent expression analysis of genes linked to insulin signalling, assessment of mitochondrial respiration and quantification of neurite outgrowth. For in vivo work DRGs from age-matched control, STZ-induced and low dose insulin-implanted diabetic rat, where hyperglycemia was not affected, were analyzed for mitochondrial protein and mRNA expression, cytochrome c oxidase activity and localization of mitochondrial Cox1. Insulin treatment (10 or 100nM for 2-24h) of cultured neurons increased AMPK and P70S6K phosphorylation. Insulin elevated mitochondrial gene expression, mitochondrial respiration and neurite outgrowth. Insulin-implanted diabetic animals exhibited correction of hind paw thermal insensitivity. In DRG of diabetic rats there was suppressed expression of mitochondrial genes, reduced cytochrome c oxidase activity and abnormal mitochondrial distribution and all were restored by low dose insulin therapy. Funded by CIHR grant #MOP-130282.

1-D -140 Changes in behavioral expressions of acute and chronic pain in aging mice are associated with altered supraspinal plasticity in Pre-Frontal Cortex.

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Advanced age is associated with increases in the prevalence of chronic pain conditions and a general dampening of many biological processes including neurological, sensory and cognitive functions. Despite the high incidence of chronic pain in the elderly, little is known about the role of aging on pain. A better

understanding of the pain experience during aging is needed. We investigated the impact of aging by comparing young (3-month) and old (24-month) male mice in a series of behavioral assays including cognitive, emotional, and sensory evaluation. First, we assessed naïve mice and determined that aging mice develop both cognitive decline and sensory hypersensitivity, which are co-morbid. Second, we observed that naïve, healthy aging mice have impaired descending inhibitory control of pain but display normal pain avoidance. Third, we investigated the impact of living with chronic neuropathic pain on behavioural measures of pain and found that older animals exhibit reduced behavioural signs . To summarize, naïve aging mice are more sensitive to acute painful stimuli than their younger counterparts, but when they live daily with a chronic pain condition, they display reduced pain behaviour. Given the apparent discrepancy in pain experience between aged naïve (hypersensitive) versus aged chronic neuropathic (hypo-sensitive) mice, we looked for signs of supraspinal plasticity by measuring levels of neurotransmitters and neuromodulators. Our results suggest that persistent pain-induced supraspinal plasticity has a different biochemical signature in young vs. old animals.

1-D -141 Brainstem Responses to Simple and Complex Auditory Stimuli in Tinnitus

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Introduction: Tinnitus can cause functional or even structural changes at cortical regions. Given the possible role of the inferior colliculus (IC) in tinnitus due to the distribution of lateral inhibition and receiving input from top-down pathways, we investigated whether tinnitus can also affect subcortical regions, mainly the IC. Methods: Auditory brainstem responses to click (cABR) and speech stimuli (sABR) were recorded in 18 individuals with tinnitus and 22 controls without tinnitus matched based on their ages and genders. All subjects had normal hearing sensitivity. Results: Latencies of cABR in waves V and Vn, as well as inter-peak latencies (IPLs) of III-V and I-V were significantly longer in individuals with tinnitus compared to the controls. Individuals with tinnitus presented significantly longer latencies of all sABR waves than the control group. The tinnitus patients also presented significant decrease in the amplitude and slope of the V-A complex and declined encoding of the first and higher formants. There was a positive correlation between V wave latency of cABR and V wave latency of sABR, as well as Vn wave latency of cABR and A wave latency of sABR both in the tinnitus and control groups. Conclusion: As a main possible generator of late waves of cABR and all waves of sABR is the IC, these findings indicate that the subcortical regions, particularly the IC, may undergo maladaptive plasticity following tinnitus. The consistency between the results of cABR and sABR indicated that tinnitus might affect the processing of simple and complex stimuli in the same m

1-D -142 Cortical Reorganization Relates to Functional Activity of Upper Limb Muscles Following Chronic Incomplete Spinal Cord Injury

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Background: Reorganization within the motor cortex occurs following spinal cord injury (SCI) and can be assessed via transcranial magnetic stimulation (TMS) by creating motor representation maps of the muscles within the cortex. While these maps have been produced in able-bodied participants, changes in maps following SCI and their relation to muscle function remains unclear. Methods: Seven SCI and eight age-matched, uninjured controls were studied. TMS was delivered over a 6x5 point anchored to the C3 electrode position on the head. Representation maps were obtained for the biceps, flexor carpi radialis (FCR), and abductor pollicis brevis (APB) muscles bilaterally by delivering 3 stimuli to each grid

point at 120% of resting motor threshold. The area, center of gravity, and overlapping area for each muscle was computed. Correlations between each map parameter and maximum voluntary contraction (MVC) of the target muscles were examined. Results: SCI demonstrated increased map areas for FCR and APB compared to controls. The locations of these maps in the SCI group were medial and lateral in the dominant and non-dominant hemispheres, respectively. Negative correlations were found in SCI only; increased area was associated with decreased MVC and muscles located laterally had lower MVC?s. Conclusions: The increased cortical territory dedicated to distal muscles in SCI may relate to the opportunity to upregulate output to denervated muscles. The relationships between map properties and MVC may provide a means to utilize TMS-evoked representations to inform rehabilitation.

1-D -143 A brain-computer interface for motor rehabilitation with multi-modal feedback in chronic stroke patient

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This study shows a BCI-based motor rehabilitation system for chronic stroke patients. The rehabilitation training consists of 25 sessions (30 minutes each session) to imagine left hand movement (80 trials) and right hand movement (80 trials). The BCI system was able to analyze the EEG in real-time and triggered a functional electrical stimulator on the corresponding left or right hand to physically enable the hand movement. Additionally an avatar hand will move accordingly on a screen if the classification result is positive. Once all the training was finished, a 9-hole PEG test was used to evaluate the improvement on the patient's motor function. For a chronic stroke patient (64 years, stroke impaired left side in Feb 2014, participated the study after 18 month), the 9-hole PEG test showed an improvement of the affected left hand movement from 1 min 30 seconds to 52 sec after 24 training sessions (healthy right hand: 26 sec). The BCI accuracy varied between 70% (session 2) to 98.5 % (session 13). The mean accuracy of the first 3 sessions was 81 % and of the last 3 sessions was 88 %. Before the training, the patient could not lift the arm to feed himself, but after the training the patient was able to reach his mouth. The idea of this system is to activate the motor cortex first using movement imagination, then the arm is stimulated to move physically which activates the sensorimotor cortex, and the patient also sees the movement which activates the mirror neuron system which is tightly coupled with the sensorimotor cortex and in the end it leads to an effective setup.

1-D -144 The role of circadian rhythms in somatosensation

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Somatosensory modalities include mechanoreception (touch), thermoreception (hot/cold), and nociception (pain). Sensory stimuli are transmitted through specific ion channels and receptors that can be activated and/or sensitized by various factors. Many of these channels have also been implicated in pain conditions, including neuropathic and inflammatory pain. Our research group has shown that patients with chronic neuropathic pain often exhibit circadian fluctuations in pain intensity, reporting significantly higher pain levels in the evening than during the day. We therefore sought to understand whether a link exists between circadian rhythms and somatosensory activity. To this end, we used standard and newer behavioural assays to measure mechanical, thermal and cold sensitivity in C57BL/6 mice. Surprisingly, we found a circadian effect only in the thermal sensitivity of naïve animals, with mice displaying a higher sensitivity at 9am than at 9pm. Pharmacological characterization of this effect by intraplantar injection of capsaicin suggests that the observed rhythm is modulated by the transient receptor potential vanilloid 1 (TRPV1) ion channel, as mice displayed a higher level of sensitivity when

injected at 9am than at 9pm. Additional data to be shown at the time of presentation will provide a more complete characterization of this circadian pattern and the mechanisms through which these effects are controlled are being further examined. Our work will lead to an increased understanding of the underlying physiology of ion channels and their link to hypersensitivity.

1-D -145 Effect of strychnine on developing Zebrafish (Danio rerio) central pattern generator: From subtle effects to active disruption of a key rhythm for swimming.

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Locomotion is a fundamental task executed by the nervous system across vertebrates. Understanding key features of locomotion is necessary for an extensive comprehension of any motor pathologies affecting gait and could lead to road maps for potential cure developments. This stereotypical activity can be described as a precise pattern of muscle activation operating at specific rhythms. These rhythms are thought to rise from a dedicated spinal network named central pattern generator (CPG). The zebrafish exhibits two signature rhythms at the larval stage: a 0.5 Hz rhythm driving the occurrence of swimming episodes and a 20 Hz rhythm driving tail beats during a swimming episode. We focus on the 20 Hz tail beat frequency and test the potential presence of oscillating mechanisms via application of various drugs during electrophysiological recordings: Strychnine (a glycine antagonist), Riluzole (a persistent sodium current blocker) and CdCl2 (a panspecific calcium channel blocker). Previous studies suggest that at 3 days post fertilization (dpf), glycinergic neurotransmission is not necessary to observe 20 Hz oscillations but is needed for left right alternation. Therefore reciprocal inhibition, a well-established mechanism for CPG, couldn?t be involved in rhythm generation at that stage. While confirming these observations at 3 dpf, our results show that strychnine completely disrupts the 20 Hz rhythm in 4 to 6 dpf fish whereas the other tested drugs had little effects. This suggests that in later developmental stages glycine plays an essential role in rhythm generation.

1-D -146 Heterogeneity of presynaptic inhibition in different populations of afferent fibers.

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Presynaptic inhibition (PI) is a very powerful form of inhibition because it constrains information transmission onto second order neurons. In the spinal cord, loss of GABAA receptor-mediated PI can produce hypersensitivity like that observed after nerve injury. There are distinct patterns of GABAergic inhibition produced in specific subpopulations of primary afferent fibers. This has been particularly well studied in muscular afferents where even collaterals of a same afferent receive differential PI. However, patterns of PI within a single afferent fiber terminal are difficult to study, specially in nociceptive C-fibers, due to their very small diameter. To overcome this limitation, we performed random-access two-photon imaging in specific subpopulations of afferent terminals selectively transduced with the genetically-encoded calcium indicator GCaMP6s. Single afferents terminals could be observed in the superficial dorsal horn in mouse spinal cord slices. We measured the dynamics of calcium accumulation in presynaptic terminals following stimulation to an attached dorsal root (DR) and used bicuculline (10 µM) to block GABAA receptor-mediated inhibition. Calcium accumulation produced by repetitive DR stimulation was enhanced when increasing the frequency of the stimulation trains. Bicuculline increased the accumulation rate of calcium only in some afferents, suggesting that not all afferents are prone to the same GABAA-mediated presynaptic inhibition. We conclude that there are distinct patterns of PI produced in specific populations of primary afferent fibers.

1-D -147 Genetic dissection of the Mesencephalic Locomotor Region: Postural tone and locomotor initiation in the resting mouse

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[1]Université Laval

Discovered in the 60s, the mesencephalic locomotor region (MLR) is characterized by its capacity to elicit locomotion upon electric stimulation. Despite uncertainties about the anatomical location of the MLR, the cuneiform nucleus (CnF), mesencephalic reticular nucleus (MRN), and pedonculopontin nucleus (PPN) are assumed to be the core of this functional region. Here, we propose to better identify and characterize the MLR using optogenetic techniques in transgenic mice. Through immunohistochemistry, tracing, and stereological techniques, we show that the locomotor brainstem (the gigantocellular reticular nucleus) receives bilateral inputs (mainly glutamatergic) from the MLR. We then recorded kinematic and electromyographic responses evoked by photostimulations (channelrhodopsin2) of either glutamatergic or cholinergic neurons of the CnF, PPN, or MRN in the resting mouse. Short photostimulations of glutamatergic neurons from either nuclei evoked short-latency excitatory responses in both flexor and extensor muscles with the largest changes in the ipsilateral flexor muscle. In contrast, short photostimulations of cholinergic PPN neurons evoked long-latency motor responses in both flexor and extensor muscles with the largest changes in the bilateral extensor muscles. Moreover, long photostimulations of glutamatergic CnF/PPN/MRN neurons initiated episodes of locomotion, while those of cholinergic PPN neurons only increased the motor and postural tone. Therefore, our results suggest distinct functional pathways involved in postural tone and locomotor initiation.

1-D -148 The roles of parvalbumin and somatostatin expressing interneurons in modulating contrast adaptation in the mouse primary visual cortex

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Contrast adaptation is a visual phenomenon induced by prolonged viewing of a high contrast stimulus, which can decrease the perceived image contrast in psychophysical tests. Neural correlates of contrast adaptation have been observed in the primary visual cortex (V1) as characteristic changes in V1 neurons' contrast response functions, but the mechanisms of adaptation are unclear. Our lab recently demonstrated that when V1 was silenced during the adaptation period by optogenetically activating GABAergic interneurons the magnitude of adaptation in V1 neurons was much smaller, and the remaining pattern of modest adaptation resembled that observed in the thalamic inputs. The current study further dissected the contribution of V1 circuits to contrast adaptation by partially suppressing V1 during the adaptation period by weakly activating either parvalbumin (Pvalb+) or somatostatin (Sst+) expressing interneurons optogenetically. Our preliminary findings indicate that neither subclass of interneurons drives adaptation directly themselves, and that the gain control mediated by activating Pvalb+ interneurons has a larger impact on contrast adaptation than Sst+ activation.

1-D -149 Modulation of Orientation Selectivity in Primary Visual Cortex via Short-term Synaptic Plasticity

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In order to detect the orientation of visual input, neurons of the primary visual cortex (V1) must integrate information from thalamic afferents. Cortical synapses exhibit several forms of short-term

plasticity (STP), but the contribution of this plasticity to the response selectivity of neurons in V1 is largely unknown. In this study, we propose that STP is a candidate mechanism by which synapses may modulate the tuning curves of orientation selective neurons. Taking as a starting point the well-established Tsodyks-Markram rule for STP, we implement a model of tuned feed-forward excitatory thalamic afferents to the superficial layers of orientation selective neurons in V1. Using the model, we examine how orientation selectivity in V1 depends on STP-based filtering mechanisms at thalamo-cortical (TC) synapses. By tuning the model's parameters, we modulated thalamic input in three distinct ways, performing either low, band or high-pass filtering, and find that TC synapses may produce broad (via low-pass filtering), medium (via band-pass filtering), and narrow (via high-pass filtering) orientation selectivity. Using Fisher information, we compare the three TC synaptic filters in predicting the accuracy of the population code of V1. We find that high-pass filtering is the only mechanism to offer a close fit to experimental data of visually evoked activity from macaque V1 recordings. Overall, the model predicts that STP sharpens tuned thalamic afferents via TC synapses performing high-pass filtering, which in turn gives rise to orientation selective responses observed in V1.

1-D -150 VESTIBULAR CONTRIBUTIONS TO ONLINE REACH EXECUTION TAKE INTO ACCOUNT LIMB BIOMECHANICS

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To reach accurately, estimates of body motion are required to compensate for spatial displacement of the limb relative to a reach goal as well as for additional forces imposed on it during body motion. Vestibular signals are important contributors to such estimates. However, the mechanisms by which they contribute to reaching remain poorly understood. The goal of this study was to explore whether the processing of vestibular signals for online reach execution involves an internal model of limb biomechanics. To address this question, we used galvanic vestibular stimulation (GVS) to selectively activate the vestibular sensors, simulating body rotation, as human subjects reached to memorized targets in different horizontal-plane directions. We compared observed GVS-induced trajectory deviations to those predicted if subjects used vestibular signals to compensate either 1) purely kinematically for the expected spatial displacement of the arm or 2) both kinematically and dynamically, taking into account the additional forces that would be imposed on the arm by the simulated rotation and its biomechanical properties. Average trajectory deviations were larger for forward and leftward reaches compared to rightward reaches, consistent with the theoretical predictions for a compensation mechanism that takes into account both reach kinematics and dynamics. The results suggest that the mechanisms by which vestibular signals contribute to online reach execution involve "smart" processing that takes into account internal knowledge of the biomechanical properties of the limb.

1-D -152 Cognitive-motor integration assessment detects impairment in varsity athletes cleared for return to play

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Our research examines cognitive-motor integration (CMI) during eye-hand coordination, something often required when a rule is used to align the required motor output to the guiding visual information. We propose that CMI provides a simple, fast behavioural measure to track functional recovery following concussion. Our previous cross-sectional research has shown CMI declines in university-level, child, elite, and adolescent athletes who have a history of concussion, but were deemed recovered. The current longitudinal study examines CMI in varsity athletes going through their return-to-play (RTP) protocol

following concussion. Participants (n=8,) were tested on two visuomotor transformation tasks using an ASUS tablet touch-sensitive computer attached to an external monitor. They made movements from a central target to one of four peripheral targets (up, down, left, right) by sliding their finger across the horizontally-placed tablet. In a direct condition, participants viewed the targets on the tablet. In a decoupled condition, participants viewed the targets on the vertically oriented external monitor, with the cursor feedback 180° reversed (requiring CMI). Athletes continued to show performance impairments (path length, movement time, and accuracy) relative to their baseline when cleared to return based on current RTP protocols. These data suggest that the current RTP protocols do not fully capture functional abilities needed for many sports, and their impairment may underlie the increased vulnerability to further concussion.

1-D -153 Connectivity and interhemispheric inhibition between motor cortices: a study with transcranial alternating current stimulation

Gabrielle Klees-Themens[1], Louis-Philippe Lafleur[1], Geneviève Lefebvre[1], Jean-François Lepage[2], Hugo Théoret[1]
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Alpha (8-12 Hz) and beta (13-30 Hz) oscillations are believed to be involved in motor control. It has been suggested that beta oscillations are involved in motor inhibition whereas alpha oscillations contribute to motor learning. Stimulating primary motor cortex at alpha and beta frequencies may modulate corticospinal excitability and motor learning. Objective : To determine whether tACS at 10 Hz and 20 Hz can modulate corticospinal excitability and interhemispheric inhibition (IHI). Methods: Thirty healthy subjects were recruited (F = 17; mean age 24, SD = 3.95). tACS was applied over bilateral primary cortex for 20 minutes at an intensity of 1mA in a sham-controlled, cross-over design (alpha, beta and sham). Twenty TMS-induced motor-evoked potentials (MEPs) were recorded from the right first dorsal interosseus muscle immediately before and after tACS. IHI was assessed in a dual-coil paradigm, consisting of a conditioning stimulus (CS) over left M1 10 ms before a test stimulus (TS) over right M1. Ten CS-TS MEPs were compared to 10 MEPs resulting from the TS alone. Results: A repeated measures ANOVA with condition (10 Hz, 20Hz, sham) and time (pre, post) as factors revealed an interaction between factors ($f = 3.51$; $p = 0.036$). Post-hoc tests showed a significant decrease in MEP size following tACS in the 10Hz condition only ($p < 0.001$). tACS had no significant effect on IHI. Conclusion: Cortical excitability of M1 at rest can be modulated by 10 Hz tACS over bilateral motor cortex. This modulatory effect could be used to modify behaviors such as motor learning.

1-D -153 Connectivity and interhemispheric inhibition between motor cortices: a study with transcranial alternating current stimulation

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interosseus muscle immediately before and after tACS. IHI was assessed in a dual-coil paradigm, consisting of a conditioning stimulus (CS) over left M1 10 ms before a test stimulus (TS) over right M1. Ten CS-TS MEPs were compared to 10 MEPs resulting from the TS alone. Results: A repeated measures ANOVA with condition (10 Hz, 20Hz, sham) and time (pre, post) as factors revealed an interaction between factors ($f = 3.51$; $p = 0.036$). Post-hoc tests showed a significant decrease in MEP size following tACS in the 10Hz condition only ($p < 0.001$). tACS had no significant effect on IHI. Conclusion: Cortical excitability of M1 at rest can be modulated by 10 Hz tACS over bilateral motor cortex. This modulatory effect could be used to modify behaviors such as motor learning.

1-D -154 Neuronal activity in feline premotor areas in the ventral bank of the cruciate sulcus during visually-guided locomotion: Limb-independent and limb-selective activity

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In both human and primates, multiple premotor areas have been identified in the frontal lobe. These areas have been characterised based on how neuronal activity parametrises movements. In cats, several cytoarchitectonic divisions have also been identified in the agranular cortex of the frontal portion of the cerebrum. These divisions could be analogous to primates' premotor areas, however, little attempt has been made to characterize them in terms of motor planning. To address this issue, we trained two cats to step over obstacles attached to a moving treadmill belt. Once the cats were overtrained, we extensively recorded single-unit activity within these subdivisions. The present report concentrates on the properties of a population of cells within the ventral bank in which we found many cells discharging before the step over the obstacle. Such step-advanced cells showed limb-independent activity and were particularly prevalent in the medial aspects of the ventral bank while more lateral areas also included cells exhibiting limb-selective activity. We propose that limb-independent cells contribute to global aspects of motor preparation, whereas limb-selective cells provide information about which limb is first to pass over the obstacle. We suggest that the ventral bank of the cruciate sulcus comprises heterogeneous subdivisions in terms of effector selectivity. Future anatomical and physiological studies are required to determine the extent to which these subdivisions correspond to the different premotor areas defined in primates.

1-D -155 Applying Optogenetics to the Feline Model in Motor Control

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Optogenetics has become a standard tool for probing circuit organisation and behavior in mice but is less easily employed in cats or primates in which it is difficult to genetically modify cell lines. However, optogenetics can be employed in such models by using viral vectors. Through appropriate techniques, it is possible to express opsins in anatomically identified subpopulations of neurons. Here, we sought to develop a technique allowing us to modulate the activity of cells projecting to the cat's primary motor cortex (M1) from other cortical areas. Using the green fluorescent protein (GFP) gene for labeling, we first evaluated the expression pattern of two adeno-associated virus serotypes (AAV6 and 9) when injected into M1. We found that AAV6 produced substantial retrograde labeling in several brain regions including the thalamus, the posterior parietal cortex (PPC) and the premotor cortex. However, to obtain strong labeling, it was essential to allow sufficient time (> 2 months) for transport and expression. In one experiment, we injected the AAV6 vector containing an hSyn-hChR2(H134R)-eYFP construct into the forelimb representation of M1. After 18 weeks of incubation, we found that we were able to optically activate neurons not only in M1, but also in the PPC. This latter finding demonstrates the feasibility of

using optogenetics to stimulate specific subpopulations of cortico-cortical neurons in the cat. Chronic instrumentation of M1 with a multi-channel optical probe showed that the responsiveness was robust and stable in the awake animal over several months.

1-D -156 CONTRIBUTION OF THE SODIUM PROTON EXCHANGER NHE6 TO NOCICEPTION

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Christianson Syndrome (CS) is a recently characterized X-linked neurodevelopmental disorder caused by loss-of-function mutations in the gene slc9a6, encoding the Na+/H+ Exchanger 6 (NHE6). The disease is associated with intellectual disability, mutism, loss of motor function and susceptibility to seizures. Interestingly, CS patients exhibit unusually high pain thresholds; the underlying causes of which have not been examined. This study aims at understanding how loss-of-function of NHE6 affects pain transmission. To this end, we examined the expression of NHE6 in peripheral and central neurons implicated in pain transmission. Additionally, we characterized the mechanical and thermal nociceptive behavior of an NHE6 knockout mouse as a model of CS. Our immunohistochemical experiments demonstrate that NHE6 is highly expressed in nociceptive, small-diameter dorsal root ganglia (DRG) neurons. Specifically, the exchanger mostly co-localized with CGRP-expressing and IB4-binding neurons and less so with large-diameter proprioceptive parvalbumin neurons. Moreover, mice lacking NHE6 display decreased responses to noxious mechanical and thermal stimuli in nociceptive behavior tests. Our preliminary results suggest a potential role for NHE6 in the proper functioning of nociceptive neurons in DRGs. Whether the decreased pain behavior is due to defect in nociceptors, dorsal horn circuits or supraspinal pain processing centers, remains to be determined.

1-D -157 Characteristics of neurones in the globus pallidus (GP) of the cat during visually-guided locomotion

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The locomotor deficits observed in Parkinson's disease suggest that the basal ganglia (BG) exert a strong effect on the control of locomotion. However, despite this, we have little information on the properties of neurones in different parts of the BG circuit during this essential behaviour. In this study we examined the discharge patterns of neurons in the globus pallidus (GP) (equivalent to the external segment of the primates' GP, i.e. GPe) of 2 cats during unobstructed locomotion and during visually guided locomotion as cats stepped over obstacles attached to a moving belt. Most neurons (N=70) showed relatively high discharge at rest (10-72 Hz) and showed either no, or relatively weak, modulation of their discharge pattern during unobstructed locomotion. When the cats stepped over an obstacle, 47/70 showed modification of their activity related to either the forelimb or, less frequently, the hindlimb. The largest proportion of modified cells (32/47, 68%) showed changes in discharge activity that were phase-locked with the activity in the contralateral forelimb when it was the first limb to step over the obstacle. One half of these cells (16/32) discharged during the step over the obstacle, while the other half (16/32) discharged up to 2 steps before the modified step. The results suggest that the GPe contains 2 subsets of cells, respectively involved in the execution and the preparation of voluntary gait modifications.

1-D -158 Distribution of P2X2 and P2X3 purinergic receptors in the head of the newborn opossum, Monodelphis domestica

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The P2X family of ATP-binding purinergic receptors (P2XR) are ion channels which subtypes are expressed in the central nervous system as well as in peripheral tissues, where they are involved in numerous functions. We have examined the expression of some P2XR subtypes in newborn and developing opossums Monodelphis domestica, a marsupial species used as a model to investigate motor systems development in mammals. Newborn opossums compare to rat embryos of 13-14 days. Previous experiments using in vitro preparations of newborn opossums have shown that motor responses to mechanical stimulation of the face are affected by application of the non-specific P2XR antagonist PPADS. In the present study, we have used immunofluorescence on fixed tissues to study the distribution of P2X2R and P2X3R in the head of newborn (P0) and neonatal opossums. From P0 to P9, P2X3R immunolabeling was observed solely in the skin covering the back of the lids and the cornea, but in no other tissues. It was no longer detected at P13. P2X2R labeling was not observed at P0, but was present at P9 in the trigeminal ganglion and the brainstem. In the latter, labeled fibers were seen mostly at the periphery, but also centrally in the metencephalon. The expression of P2X2R was strongly reduced in the previous areas at P13. These preliminary results suggest that both P2XR subtypes are expressed in early development of opossums and that P2X2R, at least, may be involved in the control of their precocious sensorimotor behaviors. The very limited expression of P2X3R makes its involvement less likely.

1-D -159 Altered Resting-State Functional Connectivity Following Isometric Handgrips in Healthy Aging

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The impact of executed hand movements on whole-brain resting-state functional networks in healthy aging remains has been pursued on a very limited basis. The current study compares the effects of performing unimanual and bimanual motor tasks on resting-state functional connectivity in healthy elderly individuals and healthy young adults using magnetoencephalographic (MEG) data. Twelve young subjects (mean age = 23.7 years, SD = 2.9) and six elderly subjects (mean age = 68.2 years, SD = 4.8) participated in the study. All subjects were right-handed and underwent three separate 5 min resting-state sessions, interspersed with two motor control tasks. MEG data were acquired and beamformer-based time series were reconstructed for 148 brain regions. The Hilbert transform was subsequently used to extract the instantaneous power and phase from four frequency bands: Alpha (8-12 Hz), Beta (13-30 Hz), 'low' Gamma (31-80 Hz), and 'high' Gamma (81-150 Hz). Functional connectivity analysis was performed by systematically computing pairwise envelope correlations between all brain regions. During the first resting-state, elderly individuals demonstrated increased functional connectivity relative to younger adults, however, during the second and third resting-state sessions, elderly subjects exhibited reduced functional connectivity (i.e., functional disconnectivity) when compared to the young adult group. Our findings suggest that unimanual and bimanual hand grips result in significant resting-state functional connectivity changes in elderly subjects but not in younger adults.

1-D -160 Mechanisms of Right Posterior Parietal Functional Connectivity to the Contralateral Motor Cortex

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The right posterior parietal cortex (PPC) plays a predominant role in visuospatial abilities, yet its influence on the contralateral primary motor cortex (M1) remains unclear. Here, we used dual and triple-site transcranial magnetic stimulation (TMS) to test the hypothesis that the right PPC is functionally connected to left M1 via two distinct interhemispheric pathways. We predicted that these pathways correlate with visuospatial performance. Eleven people participated (6 females, 25-63 years old). TMS was delivered by 3 small coils over right PPC, left PPC and left M1. Motor evoked potentials (MEPs) were recorded from right first dorsal interosseous muscle. Right PPC stimuli were set to 30, 50, 70, 90, 110, 130% of resting motor threshold (RMT). Four conditions were tested randomly with 10 trials each: M1 alone, left PPC+M1 (interstimulus interval (ISI) 5 ms), right PPC+left PPC+M1 (ISIs 5 and 10 ms), right PPC+left M1 (ISI 15 ms). In a visuospatial task, 8 participants judged subjective vertical (SV) of a rod with or without a rotated frame. The right PPC to left M1 pathway facilitated at 90% RMT ($P=0.03$), and the right PPC to left PPC pathway had a facilitatory trend at 50% RMT ($P=0.08$). SV without a frame correlated with connectivity at 90% RMT in right PPC to left M1 ($\rho(5)=0.86$, $P=0.01$) and at 50% RMT in right PPC to left PPC ($\rho(6)=0.79$, $P=0.02$). Slope of perceptual bias and connectivity correlated at 30% RMT in right PPC to left M1 ($\rho(5)=-0.89$, $P=0.007$). The right PPC connects to the contralateral M1 by interhemispheric pathways related to visuospatial processing.

1-D -161 Examining the role of TRP channels in Drosophila larval thermal preference

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The ability to sense and integrate changes in environmental temperature is vital for the survival of animals. Of the molecules required for thermosensation, perhaps the most well-known and characterized are the transient receptor potential (TRP) channels. Here we take advantage of the many tools available in the model organism, Drosophila melanogaster, in order to further examine the critical role these proteins play in thermosensation and integration. First, wild-type flies were reared at different thermal acclimation temperatures in order to determine if ambient temperatures could influence the endogenous expression of TRP channels. Using qPCR were we able to demonstrate that several TRP channels showed significant differences in expression when reared at different temperatures. We then created a thermal preference assay to examine if thermal acclimatization altered the thermal preference of third-instar larvae. Next, using RNAi to knockdown expression of several key TRP channels, we have demonstrated that reducing the expression both 'cold-sensing' and 'warm-sensing' TRP channels can significantly alter thermal preference compared to control animals. Using the Gal4/UAS system we have begun to drive expression of RNAi in subsets of tissues and cells in order to illuminate where expression is necessary for thermosensation and integration. We are also attempting to examine the endogenous expression profile of a subset of TRP channels in third-instar larval. This work was supported by NSERC and NIH.

1-D -162 The TRPV1 channel controls endogenous opioid analgesia via trafficking of beta-Arrestin2 to the nucleus

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TRPV1 channel (a.k.a capsaicin receptor) is a central player in inflammatory pain sensation. Capsaicin has been extensively used as local analgesics and there is evidence that inflammation at the periphery "primes" opioid receptor signaling. Here we investigated the functional consequence of TRPV1 activation on opioid receptor signaling and analgesia. Results: In expression systems and sensory

neurons, activation of TRPV1 induces the translocation of β-arrestin2 to the nucleus. Using BRET assay, we found that β-arrestin2 recruitment to mu Opioid Receptor (MOR) was fully abolished upon co-stimulation with DAMGO capsaicin compared to DAMGO alone. Consequently, DAMGO-induced MOR internalization was prevented by TRPV1 activation. Functionally, capsaicin was able to completely reverse the DAMGO-induced MOR desensitization measured by Cav2.2 calcium channel inhibition, an effect abolished in β-arrestin2-/- cells. In vivo, CFA injection in mouse hind paw induces inflammatory pain that progressively resolved from day 6 to day 14. This is mediated by the local release of opioids, as treatment with naloxone-methiodide, an antagonist of ORs unable to cross the blood brain barrier, delays this recovery. However, in TRPV1-/- mice, hyperalgesia was maintained up to 14 days, and naloxone-methiodide had no effect on the CFA induced pain threshold, suggesting that endogenous opioid-mediated control of pain is absent in TRPV1-/- mice. Our results show that TRPV1 regulates endogenous opioid signaling during inflammation by preventing β-arrestin2-mediated MOR desensitization.

1-D -163 Comparative analysis of allocentric visual-motor transformations between the Frontal eye fields and Supplementary eye fields of head unrestrained monkeys

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The neural underpinnings of allocentric spatial transformation are yet not completely understood. Here, we investigated the visual-motor transformations by classifying the spatial codes embedded in the visual (V) and motor (M) activities of the frontal eye fields (FEF) and supplementary eye fields (SEF) of head unrestrained monkeys. Monkeys were trained to make centrifugal gaze shifts toward briefly presented targets distributed across the neuronal receptive fields. A variable memory delay was provided between the visual stimulation and the go signal for a gaze saccade. As an allocentric task, a visual cue (intersecting vertical and horizontal lines) was presented in one of four oblique directions located 11º from the target. During the delay period, a visual mask was briefly presented while the cue was displaced by 8° in one of eight radial directions. Both monkeys show a 25% influence of the cue shift on gaze behavior (Li et al. 2016). Activities of the FEF (n = 14) and SEF (n = 8) neurons were simultaneously recorded. Using similar model-fitting as Sajad et al. (2015, 2016), the preliminary egocentric population analysis revealed that the FEF visual burst encodes the target in eye-centered coordinates (Te), whereas the movement activity was best described by gaze relative to eye (Ge). The SEF neurons recorded to date do not exhibit clear-cut spatial tuning or preference for any particular model. Further analysis is targeted on testing the allocentric models, gain fields, spatial transformations during memory delay (Sajad et al. 2016) and oscillations between both areas.

1-D -164 Linear Readout of Cortical Activity Suggests a Role for Criticality in Neural Coding

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Spontaneous neuronal activity in vitro is often characterized by network bursts, whereby a large proportion of cells are active in close temporal contiguity. In the past decade, both experimental and theoretical work have characterized the regime of these network bursts in terms of a critical state where the statistics of activity follow a power-law distribution. However, the benefits of this regime in terms of neural coding remain largely unknown. Here, we recorded from dissociated cortical neurons using multielectrode arrays and show that despite fluctuations in spontaneous activity over time, network activity over all N=60 electrodes can be described by a low-dimensional attractor with only N-1

parameters, substantially fewer than the number of parameters required for pairwise correlations (N^2). To test whether activity across different networks could be accurately discriminated, we fed population activity into a linear readout trained with a Fisher criterion. This linear readout successfully discriminated amongst different networks with less than 3% error rate. Using simulations of neural activity in a simplified branching model, we show that network activity that is near a critical regime (but not necessarily at the exact critical point) is optimally discriminated by a linear readout. Taken together, results point to a dynamical signature of cortical representations and outline forms of neural activity that are most amenable to decoding by downstream structures.

1-D -165 Auditory stimulation modulates orientation selectivity in V1

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Multisensory stimulation can have a substantial impact not only on cognitive processing but also on the basic visual perception. Non-visual input such as auditory stimuli can affect visual functioning in myriad ways. For example, anatomical and electrophysiological approaches in non-human primates (Ghazanfar & Schroeder, 2006; Driver & Noesselt, 2008) provide evidence that multisensory interactions can be observed at early stages of sensory processing. Another study by Muckli et al. 2013 highlights the existence and importance of non-geniculate input to V1 by associated areas such as auditory cortex. Further, Vetter et al. 2014 displayed through task-based approaches in blindfolded healthy adults that, by solely performing an audio task, a response in the visual cortex was observed. Therefore, primary areas such as V1 and A1 showcase high multisensory interaction predominantly of a modulatory influence in response to a complementary stimulus. In the present investigation, the effect of sound was examined on the shifts of orientation tuning curves of simultaneously recorded supra- and infragranular layer neurons by presenting a broadband noise-like auditory stimuli for 12 minutes. The recordings were performed in area17 of the cat visual cortex using tungsten multichannel depth electrode. Our data show that after the presentation of the auditory stimulus (1) A population of visual cortical neurons attain new orientation selectivity (2) Few neurons in either layer lose their selectivity and become untuned (3) Superficial and deeper layer neurons exhibit functional syn

1-D -166 Discrimination of finger flexion speed using EEG power spectral entropy

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1.Introduction. In order to reproduce smooth movements of prosthetic finger in non-invasive BCI, it is very important to comprehensively extract parameters representing the limbic movements from scalp-recorded EEG. In this study, we will predict finger flexion speed from the EEG power spectral entropy (PSE) . 2.Method. During the index-finger flexion in two kinds of speeds, we recorded 21-ch EEG, EMG and EOG. Then, we applied ICA to the EEG with 0.5-60 Hz band-pass filtering and investigated the relationship between the time course of the PSE at each electrode and the speeds. 3.Results and Considerations. It was found that at electrodes corresponding to the motor cortex, the PSE during the movement decreased in 60 % compared with that during resting, that different flexion speed led to different decreasing rate of the PSE, and that the faster flexion speed yielded the faster decrease of the PSE, while the slower flexion speed yielded the slower decrease of the PSE. Consequently, the finger flexion speed might be represented by the PSE of scalp-recorded EEGs.

1-D -167 Neural mechanisms involved in updating grasp plans: An fMRI study

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Reach and grasp plans must adapt to both externally and internally imposed changes, which have been previously investigated (Pelisson et al., 1986; Medendorp et al., 2003). However, less is known about how grasp plans are updated in light of external and internal changes (Le et al., 2014). Here, we used an fMRI-adaptation-inspired design to investigate cortical mechanisms for updating grasp plans during changes in object orientation and/or gaze location. In each trial, participants (n=7) were instructed to always fixate on one of two LEDs. An oriented object (0° or 135°) was illuminated twice. Across the two illuminations, the object was presented at the same orientation (Repeat condition) or different orientations (Novel condition). After the second illumination of the object, participants were required to grasp the object. We analyzed the second illumination period to identify areas that change the grasp plan based on: 1) feature parameters (Novel Orientation > Repeat Orientation) and 2) spatial parameters (Saccade > Fixation). Preliminary results suggest that feature parameter processing recruits left SPL, SMG, lingual gyrus, MTG and MFG, as well as right posterior-aIPS. In contrast, spatial parameter processing implicates bilateral inferior, middle and superior occipital gyri, SPL, precentral gyrus, M1, left ITG, IPL, mid-IPS, anterior precuneus, SPOC and FEF. Overall, processing of spatial properties taps into the occipital (visual)- frontal (motor) network, whereas feature properties activate areas along the occipito-temporal and occipito-parieto-frontal pathways.

1-D -168 Top-down control of sensory focus

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In senses as diverse as vision, hearing, touch and the electrosense, sensory neurons receive bottom-up input from the environment, as well as strong top-down input from a hierarchy of feedback loops originating from higher brain regions. Through connectivity with inhibitory interneurons, these positive feedback loops can exert both positive and negative control over fundamental aspects of neural coding including bursting and synchronous population activity. We show that a prominent midbrain feedback loop synthesizes a neural code for motion reversal in hindbrain electrosensory ON and OFF pyramidal cells by inactivating distinct feedback pathways during in vivo extracellular recordings. We demonstrate that synthesis of motion representations and cancellation of distracting signals are mediated simultaneously by dendritically compartmentalized feedback, satisfying accepted definitions of spatial attention. The connection between balanced excitatory and inhibitory feedback, optimized neural coding and a classic motion tracking behaviour, provides new insight into the computational roles of feedback and active dendrites in mechanisms of spatial localization.

1-D -169 The rate and temporal patterning of spikes in primary somatosensory cortex independently encode the amplitude and frequency of periodic signals like those driven by vibration

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How cortical neurons encode tactile information remains contentious. Firing rate seems to encode certain stimulus features but spike timing is also important. For vibrotactile stimulation, driven by periodic signals of 100-600 Hz, emerging evidence suggests that spike rate and timing are important. Notably, pyramidal neurons in the first somatosensory cortex (S1) fire at rates <<100 Hz. To encode high rate signals with low rate spiking, we hypothesized (1) that neurons fire on only a subset of cycles, but

do so at a preferred phase such that spike timing encodes stimulus frequency; and (2) that higher amplitude signals cause fewer cycles to be skipped, resulting in a rate-based code of stimulus intensity. We tested these hypotheses using whole-cell recordings from pyramidal neurons in a slice preparation of mouse S1 cortex. Dynamic clamp was used to simulate a high-conductance state with different noise levels. Our data confirm that spikes occur at a preferred phase of the stimulus, consistent with temporal-based coding of stimulus frequency, and that firing rate is positively correlated with stimulus amplitude, consistent with rate-based coding. However, firing rate also varied with stimulus frequency in the absence of noise, thus confounding rate-based coding of intensity, but noise abolished that relationship without disrupting the phase preference required for temporal coding. Our data suggest that spike rate and timing encode different stimulus features and that background noise is critical for enabling these two coding schemes to operate independently.

E – Homeostatic and Neuroendocrine Systems

1-E -170 Luman/CREB3-deficient mice display blunted stress responses and a disregulated HPA axis

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The secretion of glucocorticoids (GCs) is the classic endocrine response to stress in mammals. Aberrations in this response have been linked to a number of highly prevalent mental disorders such as depression as well as metabolic diseases and cancer. Understanding the underlying mechanisms is key to prevent and treat these diseases. Dissecting and analyzing factors involved in the primary stress response axis, the hypothalamic pituitary adrenal axis, will help gain critical knowledge of these mechanisms. LUMAN, originally identified through its interaction with a cell cycle regulator HCFC1, is an endoplasmic reticulum membrane-bound transcription factor that is involved in endoplasmic reticulum stress and the related unfolded protein response. Luman has been linked to the glucocorticoid response and to an increase in GR activity. Here we show that Luman-deficient mice have a blunted stress response characterized by low levels of anxiety and depressive-like behaviours in addition to low circulating GC levels. We also have preliminary evidence indicating that Luman may play a role in the cellular secretory pathway during times of high secretory demand, ie CRH release in response to stress. These results present us with a circular question regarding the cause of blunted stress response in Luman-deficient mice - is it the secretion defect that results in low GC levels leading to a compensatory increase in GR; or is it the increase in GR levels that induces negative feedback resulting in low GC level? Our current data seem to suggest that both mechanisms may exist in mice.

1-E -171 Maternal high fat diet and prenatal stress programmes neonatal behaviour and stress physiology

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The maternal environment has a profound effect on the development of offspring, including responses to stress mediated by the hypothalamic-pituitary-adrenal (HPA) axis. Maternal stress and diet program the HPA axis in a manner that persists throughout adulthood, however, studies of their effects on stress-related behaviour and physiology in neonatal life are limited. The first two weeks of life in rodents is known as the stress hyporesponsive period. During this period, the maturation of neural systems mediating the HPA axis leads to the suppression of ultrasonic vocalizations (USVs) and movement in the

presence of threatening stimuli, such as male odor. We investigate the effects of maternal stress during the last half of gestation and perinatal maternal high fat diet (HFD) on stress-related behaviour and physiology in neonatal rat offspring. On postnatal day 7, HFD pups produced fewer USVs and showed greater immobility and higher Cort levels in response to isolation alone, an effect that was further exacerbated by the presence of male odor. On postnatal day 13, only HFD pups that were prenatally stressed showed a heightened Cort response to male odor. This indicates an interaction between maternal stress and HFD to sensitize the HPA axis in the older pups. These preliminary results indicate an alteration in typical responses to stress during the hyporesponsive period of the HPA axis as a function of maternal stress and HFD exposure, which may involve changes in the regulation of genes mediating the HPA axis.

1-E -172 Differential DNA methylation in the rat brain in adulthood associated with high fat diet exposure in early life

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Maternal obesity and consumption of a high fat diet (HFD) during pregnancy are known to increase the risk of health problems in offspring during the later stages of life. HFD increases systemic and brain inflammation, resulting in an overall dysregulation of immune response. Previous work by our group showed gene expression differences of glucocorticoid and related immune genes in adolescence and adulthood in Long-Evans rats exposed to maternal HFD. These differences were not associated with current HFD consumption or differences in body weight since all offspring were provided control diet after weaning. The underlying mechanism of these differences in offspring is unclear, but may arise in part via epigenetic mechanisms such as DNA methylation. We explored this hypothesis by examining the DNA methylome, DNA methyltransferase (DNMT) activity, and the expression of epigenetic regulators and stress-related genes in the hippocampus and amygdala of Long-Evans rat offspring from rat mothers exposed to HFD during pregnancy and lactation. We found impaired DNMT activity accompanied by wide DNA methylome differences in HFD-exposed offspring. Gene ontology network analysis identified differentially methylated genes in HFD-exposed offspring implicated in nervous system regulation, cellular signaling, and metabolic regulation. Our results reveal epigenetic differences associated with the biological dysregulation in adult animals exposed to HFD in early life.

1-E -173 Effect of chronic salt intake on vasopressinergic magnocellular neurosecretory neurons in the supraoptic nucleus

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High dietary salt intake (HDSI) is considered a risk factor for elevated blood pressure and is correlated with the incidence of cardiovascular disease and stroke. Increases in osmotic pressure due to increased plasma sodium levels are detected by osmosensitive neurons in the hypothalamus, called osmoreceptors. Osmoreceptors in the organum vasculosum laminae terminalis (OVLT) send an excitatory projection to the supraoptic nucleus (SON) and activate specialized magnocellular neurosecretory cells (MNCs). These MNCs project to the neurohypophysis, from which they release vasopressin (VP) into the circulation. Recent studies demonstrate that chronic exposure of rats to HDSI excessively activates MNCs and enhances secretion of VP. However, the synaptic mechanisms underlying these increases remain poorly understood. VP-eGFP Wistar rats were subjected to a 7-day salt-loading period in which their drinking water was replaced with 2% NaCl. Whole cell patch-clamp

recordings of SON neurons were performed using an acute slice preparation that retains the OVLT→SON synaptic connectivity. Patched cells were fluorescently validated as VP-expressing using live fluorescent microscopy and then exposed to an acute hyperosmotic stimulus. Preliminary current clamp analyses demonstrate changes in firing rate and membrane potential while voltage clamp analyses detect changes in spontaneous excitatory postsynaptic current frequency. This study aims to elucidate the possible enhancement of the OVLT→SON synaptic connection as a correlate of enhanced VP secretion following HDSI.

1-E -174 Deletion of melanin-concentrating hormone receptor 1 from the accumbens nucleus increases locomotor activity

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Melanin-concentrating hormone (MCH) is a critical regulator of energy homeostasis. Transgenic deletion of its receptor MCHR1 results in leanness by increasing energy expenditure and locomotor activity. MCHR1 expression is widespread but a large proportion of MCHR1 cells are GABAergic. We tested the role of GABAergic neurons for the effects of MCH on body weight, energy expenditure or locomotor activity by selectively deleting MCHR1 from GABAergic neurons. We generated the MCHR1-flox mouse and crossed it to the vGAT-cre mouse to produce the conditional vGAT-MCHR1-KO mouse. Compared to vGAT-cre controls. vGAT-MCHR1-KO mice were 11% leaner, had 20% less body fat, 70% greater energy expenditure and 93% increase in total baseline ambulation. We found that vGAT-MCHR1-KO mice had an enhanced and prolonged response to the dopamine reuptake blocker GBR12909, which produced a two-fold increase in cumulative locomotor activity lasting more than 5 hours. In order to identify a candidate brain area supporting MCHR1 locomotor activity, we stereotaxically injected an adeno-associated virus encoding cre recombinase-mCherry into GABAergic MCHR1 brain regions of MCHR1-flox mice. Deleting MCHR1 mRNA from the accumbens nucleus increased total baseline locomotor activity by 82%. These findings show that MCH acts partly via GABAergic neurons in the accumbens nucleus to regulate body weight and energy expenditure. Furthermore, MCH signaling in GABAergic cells may inhibit dopamine transmission in the accumbens nucleus to regulate ambulatory activity.

1-E -175 Measuring the activity of hypothalamic CRH neurons during stress

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Corticotropin-releasing hormone (CRH) synthesizing neurons located in the paraventricular nucleus of the hypothalamus (PVN) control the corticosterone response to stress via the hypothalamus-pituitary-adrenal (HPA) axis. The link between CRH cell activity and the endocrine response to stress is derived from hormone measurements and indirect/proxy measures of neural activity. The activity of CRH neurons in awake, behaving rodents in response to different environmental conditions is largely unknown. We utilized a genetic calcium indicator combined with fiber photometry to measure the activity of PVN CRH neurons in vivo. A Cre-dependent AAV construct containing GCaMP6s was injected into the PVN of CRH-Cre transgenic mice. Following two weeks of recovery, an optical fiber was implanted above the PVN. Calcium changes in freely behaving mice in different conditions, such as homecage, novel environment and during footshock were recorded 7 days later. We observed a rapid and robust increase in PVN CRH Ca2+ levels in response to novel environment. This response was further increased by footshock. The activity of PVN CRH neurons is temporally locked to each footshock stimulus. Finally, we observed a slow decay of Ca2+ levels in PVN CRH neurons as mice were returned to

the homecage after exposure to footshock. Recently, our lab has shown that PVN CRH neurons are also implicated in the behavioral consequences of stress, thus describing the temporal organization and the amplitude of PVN CRH activity might lead to a better understanding of the circuit behind stress and stress related b

1-E -176 Status of a manual structural magnetic resonance imaging segmentation protocol of the hypothalamic-pituitary-gonadal axis

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The hypothalamus is a sexually dimorphic brain structure that signals to the pituitary, in turn activating endocrine glands, such as the gonads in what is known as the hypothalamic-pituitary-gonadal (HPG) axis. This axis regulates reproductive behavior and physiology, and may be involved in sexually differentiated psychopathologies. However, there is no protocol for the in vivo study of the entire HPG axis. OBJECTIVE. To develop a structural magnetic resonance imaging (MRI) segmentation protocol to study the HPG axis in vivo. METHOD. We present the status of a manual segmentation protocol of the HPG axis using structural MRI, from T1 and T2 weighted images acquired on a 3T Siemens scanner. Segmentation is done using Display 2.0 (Montreal Neurological Institute). This work extends existing protocols of the hypothalamus, to include hypothalamic subregions, such as the preoptic area, lateral hypothalamus, and the ventromedial and dorsomedial nuclei, the pituitary stalk, anterior and posterior pituitary glands, and the gonads. RESULTS. Preliminary data on 18.5 year olds (8 men, 8 women) are consistent with expected sex differences in total hypothalamic volume (men > women, Cohen?s d=0.58), and whole pituitary volumes (women > men, Cohen?s d=0.623). Intra-rater Dice kappa reliabilities exceed 0.80 for the pituitary gland. Gonadal measures include total volume, and antral follicle counts. CONCLUSION. We plan to test whether HPG axis integrity is altered in young adults exposed to prenatal maternal stress, and whether HPG structures are associated with psychopathological symptoms.

F – Cognition and Behavior

1-F -177 Determining the Evolutionarily Conserved Role of Glial Derived Lactate in Drosophila melanogaster Memory

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Glial cells support active neurons by providing them with lactate. Studies using mice, rats and chickens have provided evidence that the shuttling of lactate from glia to neurons is important for memory. However, it is unknown if glial-derived lactate affects memory in an evolutionary conserved manner. This question will be answered by assessing the role of glial-derived lactate in memory using Drosophila melanogaster (flies), an invertebrate that has been used extensively to model human diseases. Flies possess glia which function similarly to vertebrate glia. Recently, it was reported that fly brain glial support neuron survival by providing them with alanine or lactate. Here we tested the hypothesis that lactate generated by glial cells, and metabolized in neurons, promotes memory formation in flies. Courtship-Conditioning (CC) is a behavioural memory assay which tests the ability of male flies to remember prior exposure to unreceptive females. CC was used to test memory of flies which had been genetically altered to either increase or decrease expression of lactate dehydrogenase, the rate limiting enzyme of lactate production. Preliminary results suggest that flies with reduced glial lactate production have impaired memory performance; while flies with increased glial lactate production have enhanced

memory performance. These results will further understanding of the fundamental role which glia play in memory formation as well as provide a novel model to understand the role that glial-derived lactate plays during age-dependent and disease-associated cognitive decline.

1-F -178 Role of orexinergic receptors in the nucleus accumbens on food deprivation and forced swim stress-induced reinstatement of morphine-conditioned place preference in rats

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There are few effective treatments for preventing relapse. Orexins, including orexin 1 (OX1) and 2 (OX2), have been implicated in feeding, sleep, reward, and also stress-induced drug relapse. Besides, the nucleus accumbens (NAc) is an important brain area involved in stress-induced drug relapse and the function of dopamine system in this region is regulated by orexinergic transmissions. So, we evaluated the role of orexinergic receptors in the NAc on food deprivation (FD) and forced swim stress (FSS)-induced reinstatement of morphine-conditioning place preference (CPP). CPP paradigm was used to evaluate the effects of intra-NAc injection of SB-334867, OX1 receptor antagonist, and TCS OX2 29, OX2 receptor antagonist, on two models of stress-induced morphine relapse including FD and FSS. Morphine-CPP extinguished rats were divided into two main groups: one of the groups received 48-h FD and the other received 6-min FSS. Then, the animals bilaterally received different doses of intra-NAc SB or TCS (0.1, 1, 10 µg/0.5µl saline), 5 min before injection of morphine (0.5 mg/kg) to induce reinstatement. Our results showed that blockade of OX1 or OX2 receptors in the NAc significantly attenuated stress-induced reinstatement and role of OX2 receptor in FSS-induced reinstatement was more considerable than that of OX1 receptor. These findings indicate that the orexinergic receptors in the NAc have a critical role in FD- and FSS-induced reinstatement. It seems that orexin can affect the FD- and FSS-induced reinstatement of morphine by modulating neurotransmission in this region.

1-F -179 Spatial manipulations of visual and auditory stimuli in crossmodal attentional blink

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Attentional blink occurs when visual targets are in different spatial locations (Jefferies & Di Lollo, 2009). Several studies have shown crossmodal AB with auditory and visual targets (Arnell & Jolicoeur, 1999). It remains unknown how crossmodal AB might be affected by manipulating the audiovisual targets' spatial congruency. We compared unimodal and crossmodal AB effects under spatially congruent (targets at same location) and spatially incongruent (targets at different locations) conditions. In Exp 1, subjects were tested in two unimodal (visual T1-T2 and auditory T1-T2) and two crossmodal (visual T1-auditory T2 and auditory T1-visual T2) conditions with spatially congruent stimuli: visual stimuli were presented as a single stream at fixation and auditory stimuli were presented to both ears over headphones. In Exp 2, subjects were tested in the same unimodal and crossmodal conditions, but spatial congruency was manipulated by presenting separate simultaneous stimulus streams: two visual streams (left and right of fixation) and two auditory streams (left and right ears). T1 and T2 were presented either in the same (congruent) or opposite stream (incongruent). Our results show all unimodal and crossmodal conditions yielded an AB regardless of spatial congruency, but they differed in the AB magnitude. AB was the strongest in the congruent unimodal visual condition and the weakest in the crossmodal condition with visual T1-auditory T2 in both congruent and incongruent conditions. Our findings provide new insight into attentional interference across space and sensory domains.

1-F -180 Longitudinal studies of neurological symptoms in a mouse model of Werner syndrome

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Werner syndrome (WS) is a recessive disorder characterized by the premature onset of several age-associated pathologies including dyslipidemia, diabetes, hepatic steatosis, abnormal oxidative stress, cardiovascular diseases, and cancer. WS is caused by mutations in a gene encoding for a RecQ-type DNA helicase involved in different aspects of DNA repair, replication, and transcription. Although WS is considered a premature aging disorder, the association of mutations in the WS DNA helicase with neurological alterations remains poorly investigated. To examine the impact of WS on the brain, we generated a mouse model that lacks part of the DNA helicase domain of the WS gene homologue (WrnΔhel/Δhel). Longitudinal studies of neurological symptoms in male WrnΔhel/Δhel mice were conducted from 6 to 13 months of age. All behavioral results were compared with age-matched wild-type controls. Our screening with the SHIRPA, open field and elevated plus maze tests revealed that WrnΔhel/Δhel mice show increased activity at 6 months of age. Interestingly, this hyperactive phenotype of the WrnΔhel/Δhel mice was reversed upon aging due to the loss of muscular coordination and strength measured in these animals by the rotarod and wire maneuver tests. Also, aged WrnΔhel/Δhel mice developed stereotypy and reduced social novelty seeking behavior, under marble burying, prepulse inhibition and three-chambered social interaction tests. We hope to identify mechanisms leading to these behavioral alterations as to provide novel insights into the brain pathology of WS patients.

1-F -181 Differential roles of infralimbic and prelimbic cortices in contextual biconditional discrimination memory retrieval

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The two subdomains within the medial prefrontal cortex (mPFC), infralimbic (IL) and prelimbic (PL), have been shown to differentially control context-dependent behaviour. While activity in the PL has been shown to promote the expression of conditioned fear and drug seeking, IL activation has been associated with the extinction and inhibition of these behaviours. Yet, the potential roles of the PL and IL in contextually driven natural reward seeking remain underexplored. The present study sought to further examine the functional dichotomy of the mPFC in contextual control over appetitively motivated behaviour, employing a contextual biconditional discrimination (CBD) task in combination with temporary pharmacological inactivation. To this end, adult male Long Evans rats received CBD training involving the sequential presentation of two distinct auditory stimuli (X,Y) in two different contexts (A,B; different size & odor). Rats were trained to nose poke in response to the presentation of one stimulus for the delivery of sucrose reward and to withhold a nose poke response to the presentation of the second stimulus in a context-specific manner (e.g. AX , AY-; BX-, BY). Following acquisition, rats received an intracerebral microinjection of a cocktail of GABAR agonists or saline into the PL or IL, prior to undergoing a CBD training session and an extinction test. PL, but not IL, inactivation resulted in robust impairment in CBD memory, indicating that the PL, but not IL, is necessary for the processing of appetitively motivated contextual memories in natural reward seeking.

1-F -182 The influence of environmental factors on memory formation

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Learning and memory formation are affected by various environmental factors such as the time of day, crowding and/or social isolation. The mollusc Lymnaea stagnalis is useful for studying learning and memory because learning-induced behavioural changes can be traced to specific key neurons. Variability in memory forming capability has previously been reported between geographically separate populations of Lymnaea, with some strains showing enhanced memory formation compared to others. Here, we demonstrate that this variability also exists between two populations which originated from the same location, but were subsequently reared in different laboratory environments for many generations (Uni of Calgary vs. Brock Uni). Specifically, Lymnaea reared and maintained at U Calgary form long-term memory (LTM) following two training sessions, while animals reared and maintained at Brock U do not. Interestingly, Calgary animals reared from embryos at Brock U retain their stronger memory forming capability for at least two generations, though preliminary evidence suggests that this is lost by the 3rd generation. Alternatively, Brock snails reared from embryos at U Calgary demonstrate improved memory and now form LTM with two training sessions. The reason for this divergence in memory forming ability between different populations is being studied and activity within the neural circuit generating the conditioned behaviour can be examined. These studies will provide insight into how environmental factors may differentially influence memory formation across generations.

1-F -183 Methylene blue treatment rescues cognitive deficits in mice expressing active human Caspase-6 in hippocampal CA1 region

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Caspase-6 (Casp6) is abnormally activated in the classical Alzheimer disease (AD) pathologies, and correlates with lower episodic and semantic memory in aged non-cognitively impaired individuals. Transgenic expression of active human Casp6 in mouse hippocampal CA1 is sufficient to cause age-dependent cognitive deficits in the absence of classical AD pathologies. Methylene blue is an inhibitor of Tau aggregation through oxidation of cysteine residues. We recently reported that methylene blue inhibits Casp6 via oxidation of the active site cysteine. Here, we investigated whether methylene blue can rescue Casp6-induced cognitive impairments in our human Casp6-overexpresing mouse model. Methylene blue was given at 20 mg/kg/d orally in the drinking water of 18-month-old mice for 1 month. Episodic memory was measured with the novel object recognition and spatial memory with Barnes maze. Open field assessments measured locomotor and anxiety problems. Methylene blue treatment for 1 month reversed the Casp6-mediated episodic and spatial memory impairments. Locomotor problems and anxiety were excluded as possible reasons for the Casp6-expressing mice poor performance in cognition tasks. We are currently examining the brains of those mice biochemically and histologically to confirm inhibition of Casp6 by methylene blue and to determine the impact of methylene blue on inflammation and neurodegeneration. Our results suggest that in addition to preventing Tau disaggregation, methylene blue could benefit Alzheimer disease subjects by inhibiting Casp6-dependent cognitive decline.

1-F -184 Serotonergic (5-HT) Receptors Gate the Induction of Long-Term Potentiation (LTP) in the Thalamocortical Auditory System of Rats

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The neuromodulator serotonin (5-HT) plays an important role in controlling the magnitude of long term potentiation (LTP) and long term depression (LTD) in the visual cortex and hippocampus of rodents. Serotonergic fibers also innervate the rodent primary auditory cortex (A1), but the regulation of A1

plasticity by 5-HT receptors is largely uncharted. Thus, we examined the role of several, predominant 5-HT receptor classes (5-HT1Rs, 5-HT2Rs, and 5-HT3Rs) in gating in vivo LTP induction at A1 synapses of adult, urethane-anesthetized rats. Theta-burst stimulation (TBS) applied to the medial geniculate nucleus (MGN) resulted in successful LTP induction of field postsynaptic potential at thalamocortical and intracortical A1 synapses. Local, cortical application (by reverse microdialysis) of the broad-acting 5-HTR antagonist methiothepin suppressed LTP at both thalamocortical and intracortical synapses. In fact, rather than LTP, TBS elicited LTD during methiothepin application, an effect that was mimicked by the selective 5-HT2R antagonist ketanserin, but not the 5-HT1AR blocker WAY 100635. Interestingly, antagonism of 5-HT3Rs by granisetron selective blocked LTP at thalamocortical, but not intracortical A1 synapses. Together, these results indicate that activation of 5-HT2Rs and 5-HT3Rs, but not 5-HT1ARs, exerts a powerful, facilitating effect on LTP induction at A1 synapses. Thus, similar to its role in visual cortex and hippocampus, 5-HT acts as a powerful regulator of long-term plasticity induction in the fully matured A1 of mammalian species (supported by NSERC).

1-F -185 Human sign-trackers are more prone to risk, but not more susceptible to risk-promoting effects of reward-paired sensory features than human goal-trackers

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Animal research has identified sign-tracking - a propensity to attribute incentive salience to reward-predictive cues - as a possible vulnerability phenotype for addiction. In humans, only one study has been published on sign-tracking (Garofalo & Pellegrino, 2016); however cue-reactivity, which describes craving and behavioural responsiveness to addiction-related stimuli, has been extensively studied. Despite conceptual similarity, it remains unclear whether and how these putative addiction markers are related. Our aim was to determine whether sign-tracking predisposes individuals to a form of behavioural cue-reactivity - risk enhancement by rewards' sensory features. We classified 131 subjects as sign- or goal-trackers (median split) based on the time they spent gazing at the reward-predictive cue vs. the location of the impending reward in the sign-tracking paradigm adapted from the published human study. The effects of sensory feedback on risk were measured using two versions of an economic decision-making paradigm: in one, monetary rewards were paired with images of money and casino-like jingles; in the other, rewards were unaccompanied by sensory feedback. Sign-trackers were more risk-prone than goal-trackers across both versions, due to higher sensitivity to increases in expected reward value. Sensory feedback promoted risk taking across both groups, but if anything sign-trackers trended towards being less, not more susceptible to this effect. Heightened cue-reactivity (as measured by our paradigm) does not appear to be part of sign-trackers' behavioural profile.

1-F -186 Neural correlates of affective touch in mice

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C-tactile (CT) afferents are a subclass of thin, unmyelinated C fibers that convey affective touch signals to the brain. Stimulation of CT afferents is achieved through light and slow stroking of hairy skin, and is accompanied by reported feelings of pleasantness. It has been suggested that CT afferents become dysfunctional in chronic pain patients, which may account for clinical reports of pain in response to previously pleasant or innocuous stimuli. Human studies have repeatedly described CT projections to a network of brain regions that includes the insula, the amygdala, the anterior cingulate cortex and the prefrontal cortex. However, we have yet to identify a similar network in a mouse model. Activation of CT

afferents in mice has been proposed to have analgesic and anxiolytic effects. The lack of a comparable mouse network provides a challenge for animal researchers who wish to explore the therapeutic benefits of CT activation. Our current work endeavors to describe the central activational network of affective touch in mice. To stimulate CT afferents, we are using a "gentle touch" protocol in which an experimenter applies a light stroke to a mouse using a gloved finger. Preliminary Western Blot c-fos analysis shows activation of several predetermined regions of interest, including the nucleus accumbens and amygdala, both of which are involved in processing rewarding and aversive stimuli.

1-F -187 How does pimozide affect the motivational after-effect of rewarding brain stimulation?

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After rats receive free, non-contingent, rewarding brain stimulation, they become more motivated to seek out additional stimulation. There is evidence that this "priming" effect is not mediated by dopamine (DA). This finding is surprising given the well-established link between DA and reward seeking. We used a new operant method to revisit this issue. Male Long-Evans rats (n = 8), bearing electrodes aimed bilaterally at the lateral hypothalamus, were trained to lever press for electrical stimulation. A response on a setup lever triggered the extension of a reward lever, which was armed on a fixed-ratio (FR) schedule (range: FR2-30). Upon completion of the FR, a 0.5-s train of 300-500 uA, 0.1-ms cathodal pulses was delivered, and the reward lever was retracted. After a 30-s inter-trial interval (ITI), the setup lever extended, and a new trial began. Priming (2 or 10 0.5-s trains) was delivered during the ITI. Three h prior to testing, vehicle or the DA antagonist pimozide (0.1, 0.2, 0.5 mg/kg) was administered. Curves were obtained relating response vigour to the FR requirement. These curves were shifted leftward along the FR axis by pimozide, thus indicating that the drug attenuated the effect of response-contingent reward delivery on subsequent reward seeking. In contrast, pimozide failed to block the increase in response vigor produced by non-contingent, pre-trial delivery of rewarding stimulation. This latter result replicates the original demonstration that the priming effect persists even when dopaminergic neurotransmission has been disrupted.

1-F -188 Auditory ERP differences across a continuum of psychotic symptoms in non-clinical population

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Psychosis is a term given to a mental state described as a loss of contact with reality. The aim of this study was to relate early non-specific psychotic experiences in a healthy population measured with two screening tools (Prime Screen and Youth Psychosis At-Risk Questionnaire-Brief) to event related potentials (ERPs). Across the psychosis continuum, three ERP components were assessed: N1, P3 and Mismatch Negativity (MMN). Impaired N1 suppression (increased N1 amplitudes) during vocalization has been observed in psychosis. Similarly, there is evidence that P3 and MMN amplitudes are smaller in psychosis. We proposed that individuals higher on the psychosis continuum would have increased N1 and decreased P3 and MMN amplitudes relative to individuals lower on the continuum. In a talk-listen experiment, participants vocalized 'ah' sounds that were recorded and later played back. N1 amplitudes while talking were reduced as compared to listening. However, as risk of psychosis increased, N1 suppression was decreased during talking. In the second experiment, participants completed an oddball task in which P3 and MMN ERPs were elicited. Contrary to our expectation, P3 amplitudes did not relate to risk. However, individuals higher on the continuum had smaller MMNs. Finally, the combination of

ERPs across the experiments provided better risk predictability than data from either paradigm alone. These findings contribute to the development of a risk predictability model that could allow efficient assessment of psychosis risk and may improve the prognosis for psychotic disorders.

1-F -189 Executive Functioning and Emotion Processing Deficits in Attention-Deficit Hyperactivity Disorder and Bipolar Disorder

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Despite distinct differences in age of onset and core symptoms, attention-deficit hyperactivity disorder (ADHD) and bipolar disorder (BD) share cognitive and emotional processing deficits that can make differential diagnoses difficult. In order to better characterize these two disorders, we compared ADHD and BD performance on a saccade paradigm designed to probe both executive functioning and emotional processing. Performance on this task may identify subtle differences between ADHD and BD that traditional clinical assessments are not sensitive enough to capture. Healthy controls, ADHD, and BD participants performed an interleaved pro/antisaccade task (look towards vs. look away from a visual target, respectively) in which the gender of emotional faces acted as the directional cue to perform either the pro or antisaccade. Saccadic reaction time and direction error performance was significantly worse on antisaccade trials compared to prosaccade trials, with ADHD and BD groups making more direction errors than controls on antisaccade trials. The presentation of emotional stimuli, particularly negatively valenced and neutral faces, differentially affected the behavioural performance of ADHD and BD groups. The findings presented here suggest that executive dysfunction is a key deficit in both patient groups, and that it is differentially impaired when recruitment of emotional processing systems is also required. Further characterization of how these processing systems interact in ADHD and BD could be used to develop psychiatric endophenotypes to help improve diagnoses.

1-F -190 Modulation of cortical contrast response across the visual hierarchy depends on pulvinar activity

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The pulvinar is the main extrageniculate visual nucleus in all mammals including humans. Given its extensive reciprocal connectivity with the visual cortex, it allows the transthalamic cortico-cortical transfer of visual information. We still don't know what is the nature of the signals send by pulvinar to the visual cortical hierarchy. Recent data from our group indicate that inactivation of pulvinar decreases the neuronal activity in the primary visual cortex (area 17) but increases responses in 21a, a higher-order cortical area. This suggests that pulvinar can exert a different action across the visual cortex. We tested this assumption by creating a network of sequential cortical levels attached to a pulvinar-like structure to mimic the flow of neural activity from area 17 to 21a. Each component of the network consisted of an excitatory-inhibitory population of neurons in the balanced state. The input to the network was an excitatory Poisson spike train, similar to the projection from the lateral geniculate nucleus to area 17. Furthermore, we simulated the pulvinar inactivation as a global reduction of the strength of connectivity among pulvinar neurons. The simulated inactivation reproduced the effects observed in areas 17 and 21a when we enhanced the strength of the excitatory pulvinar-cortical projections from lower to higher cortical areas. Our findings suggest that pulvinar projections to the visual cortex work as a feedforward inhibition where the connectivity strength depends on the position of the target area along the visual cortical hierarchy. Supp CIHR.

1-F -191 Opioid-mediated conditioning as a novel mouse model of placebo analgesia

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One in five Canadians suffer from chronic pain, yet, chronic pain remains poorly managed. Despite the urgency for the development of effective analgesics, progress in this area has been slow due to strong analgesic responding from sham treatment. This phenomenon, called placebo analgesia has been suggested to arise from the classical conditioning of contextual cues associated with drug action and can contribute to analgesic responding in lieu of active drug treatment. Although its underlying neurobiological mechanisms remains elusive, placebo responding represents a gateway to understand and regulate the endogenous pain control system - a potential therapeutic avenue. In order to elucidate the neurobiological mechanism of placebo analgesia and evaluate its therapeutic potential, we used the spared nerve injury (SNI) mouse model of chronic neuropathic pain. Specifically, we assessed mechanical pain thresholds pre- and post-SNI; we then pharmacologically conditioned mice by coupling the conditioned contextual and tactile stimuli with an unconditioned drug stimulus, morphine. On the test day, the conditioned mice were injected with saline or naloxone, an opiate antagonist. In comparison to the naloxone treatment, saline treatment induced significant analgesia comparable to that of morphine. These results indicate that pharmacological conditioning of the opioid system is possible for neuropathic pain. This novel mouse model will allow us to identify neuronal network and substrates for opioid-mediated placebo analgesia and those involved in endogenous control of pain.

1-F -192 Stress-related Circuitry that Regulates Empathy-like Behaviours in Rodents

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Emotional contagion, the tendency to mimic and synchronize behaviours of another, is one of the most elementary forms of empathy. Previous work has found that pain behaviours are enhanced in mice by the observation of a familiar but not a stranger mouse that is also in pain. The absence of emotional contagion in unfamiliar male mice has been attributed to stress from social threat. Also it has been found that this social stress blocks empathic responses between unfamiliar mice through activation of the hypothalamic-pituitary-adrenal (HPA) axis. The primary objective of the current study was to further the understanding of the stress-related circuitry that regulates empathy-like behaviours in mice by measuring pain-evoked behaviors and examining molecular changes in predefined brain regions. We found increased glucocorticoid receptor phosphorylation for unfamiliar mice compared to isolated and familiar mouse conditions in brain areas known to be important for empathy in humans such as the prefrontal cortex (PFC) and anterior cingulate cortex (ACC). Preliminary analysis also showed an interesting correlation revealing that mice with reduced pain response display increased glucocorticoid receptor phosphorylation across conditions. These results aim to add to the limited findings currently available in understanding empathy, among other social behaviours, at the molecular level.

1-F -193 Transformation of the head-direction signal into a spatial code

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Animals integrate multiple sensory inputs to successfully navigate in their environments. Head direction (HD), boundary vector, grid and place cells in the entorhinal-hippocampal system form the brain's

navigational system that allows to identify the animal's current location. How the functions of these specialized neuron types are acquired and how their computations relate to each other remain to be understood. Firing patterns of HD neurons are influenced by the ambulatory constraints imposed upon the animal by the boundaries of the explored environment. In the post-subiculum, the main cortical stage of HD signal processing, the amount of spatial information is increased compared to their driving thalamic inputs by the combination of the HD signal with other sensory modalities. In addition, HD signal directly reach the hippocampus, likely conveyed from the thalamus. These findings demonstrate how the HD and other sensory information can be transduced into a spatial code in parallel, distributed pathways.

1-F -194 Alpha and beta oscillation at rest correlates with working memory capacities: A resting-state MEG study.

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Short-term storage and mental information manipulation capacities in the human brain are key to healthy cognition. These brain processes collectively known as working memory (WM) are associated with modulations of rhythmic brain activity across multiple brain areas and frequencies. We recorded resting state MEG and administered the Working Memory Index (WMI) from the WAIS-IV and the Spatial Addition (SA) subtest from the WMS-IV to assess WM performance in 28 participants. Resting state cortical sources for time series were compute for each subject. We calculated means of Power Spectrum Density for different frequency bands (delta, 1-4Hz; theta, 4-8Hz; alpha, 8-13Hz; beta, 13-30-Hz; gamma1, 30-59Hz; gamma2, 61-90Hz) and correlated MEG power normalized for the maximum in each frequency band at the sources level with WM performance. In order to control multiple comparisons, we applied non-parametric cluster mass analyses (p=0,001). We found statistically significant positive correlations with WMI in bilateral superior frontal, inferior parietal lobule and paracentral lobule, right superior parietal lobule, middle and inferior temporal gyrus, right pariéto-occipital lobule, right anterior cingulaire gyrus. SA correlated with right superior and paracentral gyrus and left frontal and parietal lobe. Results with WMI were specific to alpha band (8-13Hz) and results with SA are share in alpha (8-13Hz) and beta (13-30-Hz) band. These results are in line with finding in working memory task and fMRI activation during a task and at rest.

1-F -195 Contribution of perineuronal nets in the prefrontal cortex to cognitive function

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Perineuronal nets are components of the extracellular matrix which are crucial to the regulation of neural plasticity. These structures are lost in the prefrontal cortex of patients suffering from schizophrenia and our group has recently replicated this in a prominent animal model of the disorder. Unfortunately, the significance of the loss of PNNs and the regulation of plasticity in schizophrenia is not well understood. Our current work is investigating the consequences of PNN loss in the prefrontal cortex after treatment with the PNN degrading enzyme, Chondroitinase ABC. We injected this drug into the medial prefrontal cortex of healthy rats and confirmed the efficacy and specificity of this treatment using immunohistochemistry. We have found that PNN degradation results in the manifestation of several schizophrenia-like symptoms such as working memory deficits and sensorimotor gating impairment in affected animals. Furthermore, we have found evidence of increased immune cell recruitment to the affected area and changes in neuronal activity.

1-F -196 Population remapping in the entorhinal cortex and its role in mediating navigation in a novel water task in rats

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Previous work suggests that changes in extra-hippocampal network activity may trigger population remapping responses in the hippocampus. The entorhinal cortex (EC) has one the strongest projections into the hippocampus; changes in firing properties of spatially selective cells in the MEC, or context-mediated cells in the LEC, may be responsible for remapping of place cells in the hippocampus. Rats were trained to discriminate between visibly distinct platforms in the centre of opposite quadrants of a circular pool with ample distal cues. After training, the platforms then switched quadrants, or were placed in neutral (non-reinforced) quadrants in the pool. In general, location mediated more of the rats' choices within the environment than by cue identity. Following choice determination after platform switches, immediate early genes (IEGs), Arc and Homer-1a were tagged using fISH. Cells transcribing IEGs in the entorhinal cortex were quantified using design-based stereology. We found that cells activated in the entorhinal cortex after platform shifts were highly similar when the two platforms exchanged locations, and were more dissimilar when the platforms were moved to new locations. These results suggest that the entorhinal cortex may have a role in rate and global remapping in the spatial maps of CA1. This study provides further evidence to the importance of entorhinal cortex in population remapping in the hippocampus, and provides insight on how changes in location and appearance of environmental features control memory-guided behaviour.

1-F -197 Rats with intermittent intake access to cocaine in the past showed persistent susceptibility to reinstatement and more incubation of drug craving only when cocaine is injected rapidly

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Cocaine is thought to be more addictive when it reaches the brain rapidly (Allain et al. 2015). Prior work shows that in rats with continuous access to cocaine delivered over 5 or 90s, those taking rapid injections are more vulnerable to relapse (a key symptom of addiction) following abstinence (Wakabayashi et al. 2010). However, recent studies suggest that cocaine addicts take the drug intermittently within a bout of self-administration (SA), so as to produce spiking rather than continuously high brain levels of drug (Beveridge et al. 2012). Here we determined how drug speed variation influences the risk of relapse using an intermittent-access SA procedure (IntA) that achieves such spiking brain levels of drug (Zimmer et al. 2012). Rats self-administered iv cocaine (0.25 mg/kg/inj) 6h/d for 10d. During each session, cocaine (paired with cues) delivered over 5 in one group and over 90s in the other was available in 6 min bins every 32 min. One and 45d after the last IntA session, rats underwent an extinction session (6h) during which drug and cues were absent. Directly after, we assessed cue- and cocaine-induced reinstatement of lever-pressing behaviour (LPB). Cocaine intake was similar in the 2 groups during the IntA phase. Yet, on both days 1 and 45 of withdrawal, the drug cue and cocaine itself (10 mg/kg, ip) reinstated LPB only in the 5s-rats. They showed more increase of LPB between 1 and 45d compared to the 90s-rats (incubation of drug craving). Thus, exposure to rapidly rising spikes in brain cocaine levels might facilitate addiction by evoking changes in the brain.

1-F -198 A simple automated system for appetitive conditioning of zebrafish in their home tanks and studying underlying neural activation

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[1]Dalhousie University, [2]St. Francis Xavier University

Zebrafish are emerging as a novel model for studying learning and memory due to the accessibility of molecular tools, rich repertoire of behaviours, relatively simple neuronal circuits, reasonable cost, and usefulness for high-throughput screens. However, the number of behavioural paradigms that minimize handling stress and are well suited to the social nature of these fish is limited. We developed an automated learning paradigm to condition groups of adult and juvenile zebrafish rapidly in their home tanks in a standard zebrafish facility. Fish exhibited significant conditioned responses as early as the 5th trial, learning that the auditory stimulus (20 seconds of alternating half-second ascending and descending 100-1000 Hz sweeps) was a predictor for the presentation of food at the water surface at one end of the tank. Control zebrafish, for which the auditory stimulus was explicitly unpaired with food, displayed no comparable responses. Memory of the association persisted for at least 2 days after training when fish were tested either as groups or as individuals. The 2 day retention in juveniles (30 days post-fertilization) was associated with increased immunoreactivity to phosphorylated extracellular signal-regulated kinase (pERK), a known marker of neural activity, in the dorsolateral telencephalon. This simple paradigm permits scalable conditioning of zebrafish with minimal human intervention and reduced variability. In addition, these results support the use of pERK to examine the neural correlates of learning and memory.

1-F -199 Anxiodepressive-like behaviours induced by high fat feeding: particularities in female mice.

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A bidirectional relation exists between obesity and depression. We recently showed that consumption of a saturated, but not monounsaturated, high-fat diet (HFD) leads to anxiodepressive-like behaviours in male mice. This is dependent on activation of the nuclear factor kappa-B (NFkB) pathway in the nucleus accumbens (NAc), a brain region involved in motivation and reward. Although men tend to accumulate more adipose tissue in the abdominal region, the incidence of depression is two times higher in women. Still, the use of female mice in biomedical research remains limited. Aim: Study the consequences of saturated or monounsaturated high fat feeding on glucose tolerance, neuroinflammation, and anxiodepressive-like behaviours in female mice. Methods: Female mice were fed a low fat diet (17%kcal; soybean oil), a saturated fats (50%kcal; palm oil) or monounsaturated (50%kcal; olive oil) HFD for 24 weeks. Body composition, glucose tolerance, anxiodepressive-like behaviours and expression of inflammatory markers in the NAc were measured. Results: Similarly to males, only palm HFD-fed females developed anxiodepressive-like behaviours. However, metabolic impairments as well as expression of inflammatory markers and NFkB transcriptional activity in the NAc were similar in mice fed the saturated and monounsaturated HFDs. Conclusions: These results suggest that a saturated, but not monounsaturated, HFD promotes anxiodepressive-like behaviours in female mice. Contrarily to males, these behaviours do not seem to be related to inflammation in the NAc.

1-F -200 Post-synaptic expression of DCC regulates synaptic plasticity in the adult mammalian hippocampus

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[1]McGill University, [2]ETH Zurich

The netrin receptor deleted in colorectal cancer (DCC) and its ligand netrin-1 are both essential for normal neural development. Both are also expressed by neurons in the adult nervous system and enriched at synapses. Conditional genetic deletion of DCC expression from glutamatergic neurons in the hippocampus of adult mice resulted in deficits in long-term potentiation (LTP) and spatial memory; however, the specific pre- and post-synaptic contributions of DCC have not been identified. Here, we show that adult mice with selective deletion of DCC from the post-synaptic CA1 hippocampal subregion exhibit impairment in spatial memory tasks. Conversely, we show that selective genetic deletion of DCC from the pre-synaptic CA3 hippocampal subregion in adult mice does not result in impairments of spatial learning and memory. These findings support the conclusion that post-synaptic DCC at the Schaffer collateral synapse is required for the synaptic plasticity underlying spatial memory formation.

1-F -201 Orbitofrontal infusion of the T-type calcium channel antagonist Z944 impairs visual-olfactory integration on a novel rodent multisensory integration task

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Deficits in multisensory integration (MSI) are among the cognitive comorbidities associated with neuropsychiatric disorders such as epilepsy, schizophrenia, and autism. A growing body of research suggests abnormal T-type calcium channel activity may contribute to these impairments. Our understanding of the neural substrates of MSI is limited by a lack of behavioural assays to examine this cognitive process in rodents. Therefore, we employed a novel paradigm, the Multisensory Oddity (MSO) task. The MSO assesses unisensory processing and the ability to integrate information obtained from two sensory modalities to allow odd object identification. Specifically, two pairs of objects, each with two sensory features, are presented alongside an odd object, composed of one feature from each pair. In the present study, we tested whether the highly selective T-type calcium channel antagonist, Z944 (100, 500 ìM), dose-dependently altered MSO performance when administered into orbitofrontal cortex (OFC), an area critical to MSI. Rats treated with 500 ìM Z944 displayed significant MSO impairments on the visual-olfactory sensory combination. An oddity discrimination depending only on olfactory processing was not impaired by Z944 (500 ìM) infusions into OFC, indicating unisensory perception remained intact. Together, these findings suggest T-type calcium channels mediate the normal expression of MSI. Further investigation may help identify T-type calcium channels as therapeutic targets relevant to the treatment of disorders characterized by impaired MSI.

1-F -202 Spatial Distribution of Hippocampo-Cortical Interaction during Sharp-Wave Ripples

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Introduction. The coordination of cortical up-states and hippocampal sharp-wave ripples (SWR) during slow wave sleep plays an important role in the consolidation of recently acquired memories (Battaglia et al., 2004). It is based on studies in which investigators have recorded the cortical activity in a single cortical area. Therefore, the degree of correlation between multiple cortical regions and hippocampal ripples is not well known. Our goal was to investigate the spatial distribution of hippocampo-cortical interaction across several cortical regions. Methods. We used voltage-sensitive dyes and genetically encoded voltage indicators to capture brain activity with high spatiotemporal resolution. We imaged the cortical activity using wide-field optical imaging combined with local field potential (LFP) and multi-unit activity (MUA) recording from pyramidal layer of dorsal hippocampus CA1 under urethane anesthesia or during quite wakefulness. Results. We found that the activities of areas adjacent to mid-line sinus, especially retrospletial cortex (RSC), show stronger correlation with SWRs. We also grouped the

hippocampal MUA around SWRs and found distinct cortical response corresponding to each of these groups. Discussion. Our findings introduce a critical cortical region, RSC, involved in hippocampo-cortical interaction, for further investigations. Exploring how RSC and hippocampus communicate in different stages of memory processing, from encoding to consolidation, can shed light on mechanisms by which memories are formed and stored in the brain.

1-F -202 Spatial Distribution of Hippocampo-Cortical Interaction during Sharp-Wave Ripples

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1-F -203 The sulcus diagonalis and the ascending ramus of the lateral fissure: a comparison of two defining sulci of the inferior frontal gyrus of the human brain

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The sulcus diagonalis and the ascending ramus of the lateral fissure are two characteristic sulci of the ventrolateral frontal cortex of the human brain. On the surface of the cortex, the ascending ramus extends dorsally from the lateral fissure, dividing the posterior inferior frontal gyrus into the pars opercularis and the pars triangularis. The sulcus diagonalis is a vertically oriented sulcus within the pars opercularis. Given the close proximity and similar orientation of these two sulci, it can be difficult to identify them properly. The present study aims to provide a means of differentiating the two sulci accurately using magnetic resonance imaging (MRI). We labeled voxels within the sulcus diagonalis and the ascending ramus in 40 MRI volumes (1.5T) that had been linearly registered to the Montreal Neurological Institute (MNI) stereotaxic space, in order to determine morphological patterns, including relations with neighbouring sulci. We then quantified the morphological variability by generating probability maps using both surface-based (Freesurfer) and non-linear volumetric (MINC Toolkit) registration methods. The results demonstrate that the sulcus diagonalis is a relatively superficial sulcus that is less frequent than the ascending ramus. The latter is a much more reliable sulcus that consistently extends medially to reach the insula. Understanding the details of the sulcal morphology of this region, which, in the language dominant left hemisphere, is traditionally known as Broca's area, is crucial for functional imaging studies investigating speech production.

1-F -204 Automated Method to Measure Daily Mouse Routine Behavior in Health and Disease

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Evaluation of animal behavior remains time consuming and observer dependant process. We present an automated system for long-term evaluation of mouse behavior in home cage environment. We hypothesized that the sensitivity of our method will detect subtle changes of neuroinflammation on various gender and genetic backgrounds. We recorded mice in home cage environment for 24 hours a day, 4 days a week, and analyzed videos using Clever Sys HomeCage software. The acquired array of over 40 various behaviors was compared between multiple groups of experimental animals: male vs female, comparison of female estrous cycles, experimental autoimmune encephalomyelitis (EAE) - mouse model of multiple sclerosis vs. sham control, and EAE in hyperinflammatory genotypes vs. EAE. Females compared to males exhibit significantly more active lifestyle, including increased time spent hanging, remaining vertically, and walking; and decreased time eating. These differences were more pronounced in proestrous and diestrous cycles. Signs of neuroinflammation in EAE mice were the significantly increased time spent sleeping, eating, pausing, walking slowly; and the significantly decreased time spent grooming, digging, sniffing, and hanging. Automated method to measure daily routine in mice is able quantify and detect differences between male/female mice, differences of estrous cycle of female mice, neuroinflammatory conditions, as well as various transgenic manipulations. Our data suggest that this method is highly sensitive, unbiased approach to quantify long-term behavioral outcomes in mice.

1-F -205 Imaging Blindsight: A study of motion detection and MRI

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Research on the visually impaired offers a valuable model of functional brain plasticity and how sensory inputs reshape cortical activations. Following a unilateral post-chiasmatic lesion affecting the visual cortex, patients suffer a controlateral visual loss referred to as Homonymous Hemianopia (HH). Nevertheless, these patients preserve the phenomenal ability to unconsciously detect, localize and discriminate visual stimuli presented in their impaired visual field. To investigate this paradox, known as "blindsight", we have conducted a study using imaging techniques to evaluate the structural and functional impact of such lesion in an HH patient. The five following MRI scan sequences were collected: resting state, whole brain and sliced thalamic event related functional motion detection, diffusion-weighted and anatomical scans. A subject with a right hemianopia underwent a series of visual tasks to correlate "blindsight" performances with cerebral activity. When compared to neurotypical controls, we observed strong anatomical and functional differences as well as asymmetrical BOLD activations. As the main visual pathways of the lesioned side were missing, our results suggest that (1) sub-cortical pathways are responsible for processing and relaying visual information; (2) the white matter tracts of the still functioning areas increase; (3) the functional connectivity as a whole is modified. This reorganization in the structure and function of the visual pathways correlates with behavioural changes, thus offering a plausible explanation for the "blindsight" phenomenon.

1-F -206 Behavioral phenotyping of trait impulsivity with a decision-making task

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Impulsivity is a multidimensional construct representing a vulnerability factor for a variety of clinical disorders including addiction and problem gambling. Experimentally, impulsivity is typically measured with behavioral tasks including go/no-go paradigms and the Iowa Gambling Task, whereas clinical practitioners rely primarily on self-reported psychometric batteries. One example is the UPPS Impulsivity Scale, which partitions impulsivity into five sub-factors including positive- and negative Urgency, (lack of) Premeditation, (lack of) Perseverance, and Sensation-seeking. However, recent meta-analyses have revealed that behavioral- and self-report measures of impulsivity account for separate sources of variance in impulsivity-related traits, suggesting that these assessment measures are tapping into distinct and non-overlapping dimensions within a broader underlying construct. This lack of agreement represents an outstanding challenge to the utility of impulsivity as an explanatory construct in experimental and clinical domains alike. Here we present a novel decision-making task that yields a variety of quantitative behavioral and psychophysical measures related to risk- and reward sensitivity, response inhibition, and speed-accuracy preferences. We also report initial findings relating these measures to specific sub-factors of the UPPS scale, thereby bridging the gap between behavioral and self-report measures of impulsivity, as well as potentially aiding in the development of more precisely defined cognitive-behavioral phenotypes of impulsivity. Support: NSERC, FRSQ

1-F -207 Within-Litter Maternal Care Interacts with Dopamine Transporter Genotype and Dopamine-Related Behaviour in Female Rat Offspring

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Early life adversity, as modelled by artificial rearing in rodents, modifies dopamine-related behaviour, including impulsive action, behavioural flexibility, and sucrose preference. However, it is unknown whether natural variations of maternal care within the litter result in similar phenotypes. We live-coded maternal care for 30 minutes every other day across the first 7 days post-partum, and measured duration and average bout (duration/frequency) of maternal licking of differentially marked female pups. In adulthood, we tested dopamine-related behaviour of offspring with a Differential Reinforcement of Lower Rates (20 seconds; DRL-20) or behavioural flexibility task followed by a sucrose preference task. In addition, we investigated single nucleotide polymorphisms (SNPs) in dopamine receptor 2 and dopamine transporter (DAT) genes. Average bout of licking provided to individual pups, but not duration, correlated negatively with trials to reach criterion in the behavioural flexibility task and sucrose preference task after 1 hour. This correlation was evident with animals of the A/A genotype in a DAT SNP (RS13448119) but not the A/G or G/G genotype. DRL-20 performance was not correlated with maternal care or the genotypes investigated. Overall, this study provides evidence that a) average bout of licking may provide a measure of maternal care within the litter and b) some genotypes within the litter respond to maternal care more than others. Further testing is needed to elucidate mechanisms by which tactile stimulation provided by licking modifies dopaminergic signaling.

1-F -208 Physiological roles of glutamate secreted from VGLUT3-expressing neurons

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Vesicular glutamate transporter 3 (VG3) stores glutamate (Glu) in vesicles of neurons that commonly secrete other neurotransmitters, such as striatal cholinergic interneurons (CINs). In CINs, VG3 expression allows for Glu release and can facilitate acetylcholine (ACh) storage. Whether Glu released by VG3-expressing neurons has significant physiological functions beyond supporting ACh neurotransmission is

still poorly understood. We generated two mouse lines, one in which an excitatory DREADD (Drd) is expressed in VG3-positive cells (VG3CreDrd) and a second line in which we knocked out release of ACh (VG3CreFxDrd) in addition to expressing Drd. This allowed us to activate neurotransmitter secretion and start to isolate Glu released from VG3-positive cells. Upon CNO injection, we found that activation of VG3CreDrd cells caused decreased exploratory activity. However, the hypoactivity was not related to motor deficits or alterations in mood and anxiety. Moreover, elimination of ACh release in VG3CreFxDrd mice produced the same behavioural phenotypes, indicating ACh release may not impact the hypoactive phenotype. Thus, these results suggest activation of VG3-positive neurons produces the overall suppression of movement. Future experiments will investigate the brain regions involved in this phenotype and the contributions of other neurotransmitters. Ultimately, these experiments will broaden our understanding of glutamatergic transmission, specifically clarifying if Glu secretion from VG3 neurons has specific physiological functions independent of their co-transmitter.

1-F -209 The Efficacy of Oral Versus Injectable Administration of Analgesia

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Rodents are used in research to answer essential scientific and medical questions. Oftentimes, surgeries- like craniotomies- are preformed to answer these questions. As such, research institutions have established committees that set mandates regarding the administration of analgesia to laboratory rodents undergoing invasive procedures. These are typically administered via injection. Animals can experience stress from handling and the injection itself, which can alter the development of pain. Administering medication in an animal's water may be more effective at alleviating post- surgical pain since it is a less invasive, and remains readily accessible as opposed to receiving medication all at once through injection. For this experiment, we compare the efficacy of various medications, as well as saline given both orally and through injection for alleviating craniotomy pain in mice. We test these using minimally invasive measures of well being including the Mouse Grimace Scale to look at spontaneous pain, Time to Integrate to Nest Test to assess nest building behaviour, and Home Cage Scanning to look at behaviour in the home cage. Preliminary results have shown that control animals expressed the most pain behaviour on surgery day as compared to animals receiving analgesics, though injections seem more effective in mitigating the pain response than oral administration. Carprofen and saline injections had the same effect on animals, where these animals expressed higher pain levels than control animals by 72 hours indicating that injection stress may hinder healing.

1-F -210 Environmental enrichment increases resilience to aversive social stress in mice

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Environmental enrichment during adolescent can increase social contact, increase physical activity and reduce risk of developing depression like behavior. Enrichment can also increase neurogenesis that associate with learning memory and stress responsivity. In the study, we examined how environmental enrichment can alter gene transcription in ventral dentate gyrus, a brain region associates with emotion and neurogenesis, influence the aversive impact of emotion eliciting stimuli in mice, by using RNA-sequencing method. Animals were raised in either standard housing condition or enriched housing condition until postnatal day 80. Animals were then examined the reactivity to social attack stress. The result showed that enrichment significantly suppressed depression like behavior by measuring the social interaction test after the social attack stress. We identified 275 genes differentially expressed between

resilient animals that experience of standard housing condition and the resilient animals that are from enriched housing condition. A pathway analysis using MetaCore from Thomson Reuters suggested that an enriched cluster of these genes is involved in neurogenesis. Transcription factor binding site data showed that ESR1 and OLIG2 are two major transcription factors that might control the expression of differentially expressed genes. These data provide evidence that environmental enrichment affects neurogenesis which might play important role in affecting emotion. This work was supported by funding from Ludmer Centre for Neuroinformatics and Mental Health and by Hope for Dep

1-F -211 The effects of maternal separation and variable unpredictable stressors on behavior, neuropeptide Y and gut microbiota composition.

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Introduction: Changes in gut microbiota composition have been associated with changes in behavior. Stress is known to alter behavior and gut microbiota composition. However, it is unclear whether gut bacteria can affect vulnerability to stress. Methods: Newborn SPF C57BL/6 mice were subjected to maternal separation (MS) or were left undisturbed (controls). At week 9, some mice were exposed to variable unpredictable stressors (VUS) for 7 days. Thus, 4 groups of mice were used: A) Control n=28, B) MS only n=29, C) MS+VUS n=17 and D) VUS only n=17. Behavior was evaluated using standard behavioral tests. Serum neuropeptide Y (NPY) and cytokines were measured by ELISA. Microbiota was analyzed by 16S rRNA Illumina. Results: Compared to controls, mice exposed to stress (MS, VUS, MS+VUS) displayed increased exploratory and depression-like behavior when assessed by step down, light preference and tail test suspension tests, respectively. Proinflammatory cytokines were increased and NPY levels decreased in MS+VUS mice compared to controls. VUS caused major changes in microbiota profiles, which was further accentuated by previous MS. Overall, relative abundance of Bacteroides and Firmicutes was strongly correlated with NPY levels. Conclusion: Both early life stress and VUS in adulthood induce depression-like behavior in mice. However, their combination appears to confer lower vulnerability to stress. This is accompanied by changes in gut microbiota and serum NPY levels, suggesting these factors may play a significant role in the observed behavioral profiles.

1-F -212 EEG functional connectivity during a working memory task in children with learning disorders

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Working memory (WM) deficits are a main issue in learning disorders (LD). We compared the EEG functional connectivity of LD-children with healthy controls during a WM task. 19 LD and 21 controls (Ctrl) performed a version of the Sternberg WM task. Children had to remember 4 digits: in a light load condition (LLC) the digits were the same; in a heavy load condition (HLC) they were different. EEG was recorded by the 10-20 system. The current distribution at the sources was estimated (s-Loreta). 18 ROIs (network nodes) were selected based on a principal component analysis. A measure to find direct paths of causal information flow between ROIs (isolated effective coherence, iCOH) was applied. Results: LD-children had less correct responses than controls at the HLC. There were more differences in connectivity between the groups in the HLC. Ctrl connectivity patterns coincide with the expected WM related brain organization. LD children under-recruit left frontal areas, do not show fronto-parietal connections but greater bilateral connections between frontal areas (mostly inferior and orbitofrontal)

and involve the right mid-temporal gyrus. These may be compensatory mechanisms to attempt to overcome their limitations due to the task difficulty. WM is fundamental to school learning, and these results in LD-children could help to explain the WM deficits that might contribute to the poor performance in academic abilities like reading, writing and mathematics. Special thanks to H Belmont, L Casanova, ME Juárez, T Álvarez, S Cárdenas, M Roca, PAPIIT-IN204613, and CONACYT-251309-597545.

1-F -213 Deep Brain Stimulation improves spatial memory in an Alzheimer's Disease mouse model

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Electrical deep brain stimulation (DBS) has been suggested to be a potential therapeutic approach to rescue normal memory function in Alzheimer's Disease (AD). AD is a neurodegenerative disorder which has been linked to amyloid beta aggregation, marked memory deficits and early hippocampal degeneration. This study aims to identify memory-facilitation mechanisms of fornix DBS in the J20 transgenic AD mouse model (PDGFB-APPSwInd) by examining electrophysiological recordings of the CA1 hippocampal region. Baseline LFP recordings of CA1 were collected in 3 to 4 months old mice during awake and sleep states, and 24 hours after DBS treatment. Sham and experimental groups were tested in Passive Avoidance and Novel Place Object tasks to assess spatial memory performance. We show that J20 mice display a significant impairment in memory in the Passive Avoidance task as measured by the latency to enter the dark chamber, and in the Novel Place Object, evaluated by the Recognition Index. Applying chronic Theta-Burst DBS to the fornix during the 24 hours after the initial learning of Passive Avoidance and during 3.5 hours after the Novel Place Object's sample phase had a rescuing effect on memory. We intend to examine the relationship between the stimulation, behaviour and CA1 hippocampal oscillations to elucidate the modulatory effect of fornix DBS on the memory network.

1-F -214 Temporal dynamics of amygdala striatal communication during risk/reward decision-making

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Assessing costs and benefits associated with different options that vary in terms of reward magnitude and uncertainty is an adaptive behaviour which motivates us to select the optimal course of action. Previous studies using reversible inactivation have shown that the basolateral amygdala (BLA) to nucleus accumbens (NAc) pathway promotes choice towards larger, riskier rewards. Neural activity in the BLA and NAc show distinct, phasic changes in firing prior to action initiation and following action outcomes. Yet, how temporally-precise patterns of activity within BLA-NAc circuitry influences choice behavior is unclear. We assessed how optogenetic silencing of BLA projection terminals in the NAc altered action selection. Rats were well-trained on a probabilistic discounting task. During testing, 5-7s pulses of light were delivered to suppress BLA inputs to the NAc during specific task events; during a "prior to choice" period or different "choice outcome" periods. Silencing BLA-->NAc terminals prior to choice reduced selection of the more preferred option, suggesting prior to action selection, this circuit biases choice towards more preferred rewards. In contrast, silencing during reward omissions increased risky choice, whereas silencing during rewarded outcomes did not alter choice reliably. Collectively these data clarify how patterns of activity in BLA-NAc circuitry convey different types of information that guide optimal action-selection in situations of reward uncertainty.

1-F -215 Modulation of probabilistic discounting and reversal learning by dopamine within the medial orbitofrontal cortex

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The medial orbitofrontal cortex (mOFC) monitors probabilistic action-outcome associations and biases decisions related to reward uncertainty. Inactivating this region in rats alters both risk/reward decision-making and probabilistic learning. The mOFC receives dopamine (DA) input, yet, how DA contributes to efficient reward seeking has been virtually unexplored. Here, we assessed how mOFC DA receptors may modulate decision-making in the face of probabilistic outcomes. Specifically, we assessed the effects of intra-mOFC infusions of D1 or D2 antagonists on 1) risk/reward decision making using a probabilistic discounting task and 2) probabilistic reversal learning. Our results indicate that mOFC D1 receptors mitigate sensitivity to non-rewarded actions, as blockade of these receptors reduced risky choice by increasing lose-shift behavior. Blockade of D2 receptors increased risky choice by increasing win-stay behavior. On the other hand, blockade of D1 receptors impaired, while blockade of D2 receptors facilitated probabilistic learning. Together, these findings highlight dissociable and opposing roles for DA D1 and D2 receptors within the mOFC in guiding behavior in different situations involving reward uncertainty. Elucidating how mesocortical DA influences action selection will expand our understanding of the mechanisms regulating optimal and aberrant decision-making.

1-F -216 Dorsomedial striatum D1 and D2 receptors have opposing roles in approach-avoidance conflict decision making

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The dorsomedial striatum (DMS) is mainly composed of medium spiny neurons (MSNs) expressing dopaminergic D1 (D1R) or D2 receptors (D2R), which have recently been linked to the control of motivated behaviors. It has been shown that DMS D1R activation elicits reinforcement while D2R activation induces punishment, suggesting opposing functions for the MSN subpopulations. However, an investigation of DMS MSNs in the context of learned approach-avoidance conflict decisions, during which the animal experiences competing motivational signals compelling both approach and avoidance of a stimulus possessing both positive and negative incentive properties, is yet to be elucidated. The present study addresses this question by utilizing a mixed-valence conditioning paradigm to examine the effects of DMS D1R and D2R antagonism on approach-avoidance conflict behavior. Rats were trained in a three-arm radial maze to associate visuo-tactile cues with sucrose, shock, or neutral outcomes. Following conditioning, rats were microinfused with SCH23390 or Sulpiride in the DMS. Exploration time was then assessed in a conflict test where rats freely explored two maze arms containing either a neutral cue or a superimposition of the appetitive and aversive cues under extinction conditions. Our results revealed that D1R antagonism decreased preference for the mix-valenced arm, while D2R antagonism had the opposite effect, enhancing preference for the arm. Our results indicate that DMS D1R and D2R are oppositionally involved in approach-avoidance processing when the valence of the outcome is uncertain.

1-F -217 Magnetic stimulation of the supplementary motor complex delayed response processing in a go/no-go task in men

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The supplementary motor complex (SMC) is known to be active during response selection, but whether or not it has a role in suppressing unwanted response and/or in the activation of the correct response remains unclear. Contradictory results about the implication of the SMC in these processes were obtained in functional imaging and transcranial magnetic stimulation (TMS) studies, mostly overlooking the effect of gender. This study aimed to explore whether the SMC is involved in the response and/or the inhibition processes in a go/no-go task taking into account the gender. Sixteen adults (8 men) performed a go/no-go task (50% go) while receiving dual TMS pulses at 60 ms interval either over the medial supplementary motor area (SMA) and the pre-SMA border or over the medial parieto-occipital cortex (control). The first pulse timing was based on the subjects' RT distribution onset (mean: 129 ms). For no-go trials, we analyzed the proportion and latency of the errors and partial errors while, for go trials, we looked at the premotor and motor time. The premotor time was longer when the pulses were applied over the SMC, but only for men. No other significant effects were noted. Disturbing the SMC with TMS has delayed the response process in men without affecting inhibition, challenging the hypothesis of an implication of the SMA and the caudal part of pre-SMA in this process. Gender differences in regional brain activation often observed during behavioral tasks (including response inhibition task) may be an avenue to further explore to explain the non-significant effect in women.

1-F -218 The effects of nicotine on cognitive function across the menstrual cycle in non-smoking women

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Changes in cognitive function across the menstrual cycle (MC) have been observed in numerous studies, but not much is known about implication of nicotine in this effect, despite the fact that neuropharmacological nicotine-estrogen (E) interactions have been reported. Different levels of E and progesterone (P), hormones that fluctuate during the MC, are associated with changes in cognitive performance. High levels of E are linked to improved performance on working memory (WM) and emotion processing tasks, while low levels are associated with enhanced viso-spatial abilities. Nicotine is reported to increase cognitive performance, but results in non-smokers are equivocal. In the present study, we investigated the effects of nicotine on cognition across the MC, in healthy non-smoking women. Participants were tested twice (4 mg nicotine gum and placebo condition) in three phases of their MC (early follicular, late follicular, mid luteal) and completed WM, verbal memory, emotion identification, and visuo-spatial processing tasks. Preliminary results suggest that administration of nicotine leads to the overall diminished performance on the WM across MC, while other cognitive domains remain unaffected. WM function was best during the mid-luteal phase in the placebo condition, but nicotine interfered with it to the greatest extent during this time. Nicotine's deteriorating effect on WM in non-smoking women is inconsistent with previous results in men. We are in the process of collecting more data and updated findings will be presented during the conference.

1-F -219 Role of medial septum cholinergic neurons in memory consolidation during REM sleep

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Spatial memory consolidation has been suggested to occur during rapid eye movement sleep (REMS), since disrupting Medial Septum (MS) GABAergic neurons during REMS has recently been shown to induce defects of spatial and contextual fear memory. Although previous study suggested that MS cholinergic neurons fires during REMS there is yet no data supporting that these neurons are implicated in memory consolidation. In this study, we examined the effect of MS-cholinergic neurons silencing on

hippocampal activity during REMS and its consequences on the consolidation of contextual fear memory. To inhibit cholinergic neurons in the MS, ChAT-Cre mice were injected with the inhibitory viral construct AAVdj-ArchT (4) or a control, AAVdj-eYFP (3) and implanted with an optic fiber for optogenetic inactivation. Three weeks later, mice received contextual fear conditioning (30s of cue tone followed by 50uA of electric foot shock) and were then returned to their homecage. Optogenetic silencing was performed specifically during REMS for a 5hr period following the conditioning. On the next day, contextual and cue memory were tested. Optogenetic cholinergic silencing during REMS impaired contextual memory (91.1±9s) compared to the control group (140.5±21s, Mann-Whitney, p=0.04) but the freezing time during the cue fear memory test was not significantly different between the cholinergic silencing ArchT (178±22s) and the control eYFP (150.2±27s, mean±sem) injected groups (p=0.6). Our study demonstrates that cholinergic neurons of the MS are necessary for context memory consolidation during REMS

1-F -220 Objects devoid of edge information yield depth cue invariant representations in the ventral pathway

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Edges are thought to be the primary source of visual object information in a scene. Computational models of object recognition that utilize local edge information successful carry out diverse visual tasks such as identification, categorization, and recognition. But humans can recognize objects that are devoid of edge information?depth cues, such as texture, binocular disparity, and structure-from-motion (SFM) are non-edge (second-order) source of object information. Are human visual object representations inherently tolerant to non-edge cues? Using 1mm resolution fMRI, we measured the ventral responses to objects of different categories defined purely and uniquely by a non-edge depth cue. To compare representations, we trained classifiers on object classification based on fMRI responses to one depth cue which then successfully discriminated object responses elicited by a different depth cue. We further characterize the object representational similarity across depth cues and found that not only does the human object recognition system representing objects defined by non-edge cues, but representations are tolerant to variations in the non-edge depth cues.

1-F -221 Relationship between the modular structures of BFCNs and individual variability in foreign language learning ability

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Objective:The present study aimed to investigate the association between changes in the modular structures of brain functional connectivity networks (BFCNs) and individual variability in foreign language learning ability. Methods:Six healthy Japanese students (all male, age range: 16-21 years) completed both pre- and post-training EEG sessions and examinations in English words. BFCNs were constructed for pre- and post-training data. Training sessions required participants to attempt to memorize 200 pairs of the same English words as those in the examinations and their Japanese meanings. The connectivity between any two different electrodes (nodes) was calculated by determining the synchronization likelihood (SL) of the EEGs. An edge connecting the two nodes was drawn when statistically significant differences in SL values were observed between successful and unsuccessful trials. The BFCN was decomposed into two nonoverlapping modules by the optimization of the quality function Results and Conclusions:BFCNs for the pre-training data were higher in edge density than those for the post-training data, though this difference was not statistically significant. Moreover,

changes in the composition of modules of the BFCNs were associated with the individual difference between two English-word examinations in scores.

1-F -222 SLEEP DEPENDENT DECLARATIVE MEMORY RECONSOLIDATION IN HEALTHY YOUNG ADULTS

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Introduction: Declarative memory is defined as our capacity to acquire facts and events that are subject to conscious recollection. After the encoding phase, new memories undergo off-line transformations, which allow the initially labile traces to become fixed into the physical structure of the brain; called consolidation. There is accumulating evidence that once a consolidated memory is reactivated or retrieved, the latter goes through a reconsolidation process during which it can be degraded, maintained or enhanced. In the present study, we sought to answer the following question: Are retrieved consolidated traces susceptible to disruption by the same type of information? Method: We developed a task based on work by Sonni et al. (2015), in which subjects were required to learn the location of 36 everyday objects images located on a computer screen. 33 healthy subjects (25.03 ± 3.66) participated in this study. Group 1: Interference (16 subjects, 11 females); Group 2: control (17 subjects, 11 females). Results: We found that the administration of the matrix B after recall of the first matrix (Group 1) interfered with reconsolidation of the memory, and thus significantly increase the amount of forgetting seen in the retest session. In contrast we could not find any interference effect in the control group. Conclusion: Our results confirm the reconsolidation hypothesis for declarative memory, but further work is needed to identify whether the neural and neurophysiological substrates mediating reconsolidation are the same or different from those involved during consolidation.

1-F -223 To attack or to defend? Resolution of response competition by the Basal Ganglia.

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The basal ganglia (BG) are vitally important component of the vertebrate brain that has changed little over the ~400 million years of brain evolution. In humans the BG are associated with numerous neurological and psychiatric conditions including Parkinson's disease, schizophrenia, obsessive-compulsive disorder and numerous addictions. Many of these conditions can be interpreted in terms of 'selection-failures'. We considered the view of BG as a generic selection mechanism. To test this hypothesis we exploited the spatial separation of two exclusive behavioural systems in different regions of rat superior colliculus (SC) that contribute to separate sub-cortical loops through the BG to understand how they operate when animals are deciding between exclusive and conflicting responses. We used an anatomically based neural activity marker (in SC, thalamus and striatum) and retrograde tracer to examine interactions between the competing functional loops when the food deprived-rat was exposed to both predator and prey simultaneously. We also investigated the neurotransmission modulation (GABAA agonist) at strategic locations of the competing loops to suppress or boost the activity of one of the competitors and the animal's decision biased away from or towards that competitor's response. We suggest that tecto-thalamic-striatal projections are functionally segregated and provide an actual copy of event localization in the world (mainly the unexpected ones), which can require attention, and the BG select the impulses based in the salience weight.

G – Novel Methods and Technology Development

1-G -224 LCM-RRBS: A novel PCR-amplicon based method compatible with post-mortem samples

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Throughout neurodevelopment, spatiotemporal control over gene expression by epigenetic regulation of promoters and enhancers results in a complex heterogeneity of cell types within the mammalian brain. Thus, while a wealth of studies have investigated transcriptomic and epigenomic alterations underlying the neurobiology of psychiatric illnesses, the use of bulk-tissue homogenates have masked their ability to determine cell-type specific molecular dysfunctions. RRBS is a widely used technique for the analysis of genome-wide methylation patterns, in regions of high CpG content, at the level of a single nucleotide. There are, however, many disadvantages associated with traditional RRBS; including, it?s reliance on costly methylated adaptors, fragmentation of libraries during bisulfite conversion, high gDNA input requirements, as well as duplicated reads. Here we describe a simple, PCR-amplification directed RRBS pipeline that ameliorates the need for adaptor based library construction. Briefly, our PCR-amplicon RRBS protocol involves three steps, MspI digestion, bilsulfite conversion and PCR amplification with uniquely designed primers integrating locked nucleic acid technology. Preliminary sequencing data is of comparable quality as RRBS employing traditional library construction. In extension to this, our pipeline is capable of amplifying bisulfite converted gDNA from ~350 pyramidal cells captured from post-mortem samples using LCM. The utility of this protocol is its utility in allowing for the investigation of cell-type specific alterations underlying various illnesses.

1-G -225 Diffusion weighted tractography in the common marmoset monkey at 9.4 T

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The common marmoset (Callithrix jacchus) is a small New World primate that is becoming increasing popular in the neurosciences as an intermediate research model between human and rodents. With several major disorders characterized by alterations in neural white matter (e.g., Alzheimer's, schizophrenia) proposed to be transgenically modelled using marmosets, the ability to reliably isolate and characterize major white matter fiber tracts with MRI will be of utility for evaluating structural brain changes related to disease processes and symptomatology. Here, we propose a protocol for isolating major white matter fiber tracts in the common marmoset using ultra-high field MRI (9.4 T) diffusion weighted imaging (DWI) data. Using a high angular resolution DWI (256 diffusion encoding directions) sequence collected on four anesthetized marmosets, we provide guidelines for manually drawing fiber tracking regions of interest based on easily identified anatomical landmarks in DWI native space. These fiber tract isolation protocols are expected to be experimentally useful for visualization and quantification of individual white matter fiber tracts in both control and experimental groups of marmosets (e.g., transgenic models). As disease models in the marmoset advance, determining how macroscopic white matter anatomy is altered as a function of disease state will be relevant in bridging the translational gap between human and rodent models.

1-G -226 Elucidating the role of lncRNAs in neuronal survival

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Long non-coding (lncRNAs) are found in every branch of life, implying that they play essential roles for normal cellular function. However, as lncRNAs show dynamic expression, and bind protein, RNA, or DNA, their functions and mechanisms of action have been difficult to study. With the recent advances in RNA sequencing, the number of lncRNAs has increased exponentially, and 40% of lncRNAs are specifically expressed in the brain, implying that neurons may be highly dependent upon lncRNAs. In vivo genetic screens are essential to study gene function in an unbiased manner and many tools have been developed to use them in mammalian organisms. We propose to use such screening to understand the functions of lncRNAs in neurons. To conduct our screen, the CRISPRi methodology will be used to target lncRNAs that are specifically expressed in adult striatal medium spiny neurons (MSNs). As a test case, we will conduct a loss-of-function lncRNA screen around viability of MSNs to identify lncRNAs essential for neuronal viability and those modulating Huntington's disease toxicity. MSNs are an ideal first neuronal cell type to target, as the striatum is a relatively homogenous brain structure. Our work will be the first to probe on a genome-wide level the function of lncRNAs in the mammalian brain. In its first iteration, we will look at the simplest screening phenotype: viability. However, once our screening pipeline is established, we will be able to screen around other lncRNA loss-of-function phenotypes, including gene expression and splicing.

1-G -227 Timing and Dynamics Comparison Between Exponential, Quadratic, and the New Cubic Integrate & Fire Models

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Non-linear Integrate and fire (NIF) models are useful for their ability to predict spike times while being easier to analyze than biological models. But different NIF models have their own benefits and downfalls so choosing the correct one requires careful analysis. The two most popular NIFs are the exponential integrate and fire (EIF) and the quadratic integrate and fire (QIF). The EIF is a good neural approximation, but is mathematically difficult to analyze. The quadratic integrate and fire (QIF) is simple mathematically, but its dynamics do not match that of the EIF. Therefore, a third alternative should be considered: the cubic integrate and fire (CIF). The cubic function is already successively used as a transmission function in bidirectional associative memory neural networks and requires very little modification to produce a spiking model. All three models are canonical type I models with stability at both resting and spiking states and their firing frequency is based on input strength. A benefit of the CIF is its ability to easily modify both the dynamics and timing because the rheobase can be modified along both the x- and y-axes. Before the three models are compared, all models are set to have the same resting potential, rheobase y-value, critical voltage for spike initiation, and spike threshold. The CIF is faster in spiking than QIF but slower than EIF. The change of membrane potential also falls between QIF and EIF. Overall, the CIF is an excellent model to choice because it has both the mathematical simplicity and neural dynamics.

1-G -228 Design of a specific SOFA-ribozyme to target the tauopathies

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One of the main causes of tauopathies is the presence of neurofibrillary tangles (NFT). NFT consist in intracellular aggregation of abnormally hyperphophorylated protein Tau. Several studies have shown that NFT are associated with the pathogenesis of neurodegenerative disorders and neurotoxicity. Moreover, it has been demonstrated that decreasing the level of Tau protein could prevent cognitive deficits in mouse models. Based on these studies, our hypothesis is that reducing the level of Tau

protein in the brain could decrease the NFT toxicity and delay the pathology. Our objective is to design a molecule that will target directly Tau mRNA. We are developing the SOFA-delta (Specific On/Off Adaptor) ribozyme, able to cleave the Tau mRNA. Our ribozyme is composed of three components: the blocker, the biosensor, and the effector. In absence of Tau mRNA, the blocker inhibits the enzymatic reaction. So the ribozyme stays inactive in "Off conformation". In presence of Tau mRNA, the biosensor binds with a specific sequence on the Tau mRNA, induces the "On conformation", and the effector cleaves the mRNA. We have designed delta-ribozymes that can target all the Tau isoforms. In this project, we first synthesize the delta-ribozyme by molecular cloning. Secondly, by transfecting it in neuronal cells we characterize its effects on Tau mRNA and protein by PCR and Western-blot. Finally, we will produce AAV viruses to express our ribozymes in mouse brain and evaluate its effect on cognitive function. Thus, we expect a decrease of Tau mRNA, NFTs, and a reduction on behavioural deficit.

1-G -229 Comparison of various preparation methods for the study of tau protein phosphorylation by immunohistochemistry

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Hyperphosphorylation and aggregation of Tau protein is a histological and pathological marker of Alzheimer disease. To study the phosphorylation of Tau, brain of mice models are often examined by immunohistochemistry. However, the best method of fixation is not known. The objective of this study was to compare different fixation and sectioning methods to determine which one gives the best results by immunohistochemistry. Three different mouse lines were used: non-transgenic mice (B6 model), mice with a mutation on Tau protein (P301S model) and hTau mice (express human tau without mutation on a murine Tau KO background). We first compared fixation by immersion of non-transgenic mouse brains (with or without hyperphosphorylation) in Bouin's solution vs in 4% paraformaldehyde (PFA). Both methods were tested with or without saline perfusion before fixation, and brain fixation was performed at either 4°C or at room temperature. Paraffin embedding and sectioning was following. Finally, perfusion with Bouin or PFA 4% followed by immersion in the same fixative was tested at 4°C. Our preliminary results indicate that the fixation by immersion with Bouin' solution kept at 4°C seems to be the best method to see phosphorylation of Tau and avoid degradation. We also observed that perfusion before fixation gave poor results due to dephosphorylation of proteins in post-mortem brain. In conclusion, our results show the importance of choosing the right fixation method for the study of Tau protein to be able to see optimal signal of phosphorylation and obtain better results.

1-G -230 A rapid method for quantifying the relative intensity of immunofluorescence over large cortical regions

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The quantification of fluorescent-labelled cortical components (e.g. cell bodies) has largely been carried out in two ways: a stereological approach where a subset of neurons or other cortical structures are manually counted with extreme precision; or the average intensity of the fluorescence signal is measured at high magnification, using confocal microscopy. Although useful, both approaches are time consuming and limited in scope, restricting the adequate and accurate sampling of cortical areas and of specific cortical layers. Recently, advances in the computerized processing of tiled images have permitted the examination of large regions of the cortex. Despite this substantial increase in available

data, the field currently lacks quantitative approaches for the analysis of immunofluorescence on such a scale. The present study has provided a simple method for this purpose by modifying an approach used for brightfield cytoarchitectonic analysis by Mackey and Petrides (2009). The relative intensity of VGAT, VGLUT1 and VGLUT2 fluorescent antibodies in areas MT (middle temporal) and MST (medial superior temporal) of the rhesus macaque cortex was measured using minimally processed widefield images, sampling lines, and normalized data. This new, simple method can rapidly quantify changes in the relative intensity of the fluorescence signal in large regions of interest across the whole cortical depth as well as within particular cortical layers. This approach can aid in rapid, initial assessments of areas to guide future, more detailed analyses.

1-G -231 Differential Diagnosis of Epilepsy and Psychogenic Non-epileptic Seizures

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Distinguishing adults with epileptic seizures (ES) from those with psychogenic non-epileptic seizures (PNES) is a challenging differential diagnosis. The gold standard is in-patient video EEG monitoring. Although neuropsychological testing can enhance the clinical decision making, research on its diagnostic power produced equivocal results. The goal of the present study is to examine the discriminant power of cognitive tests when applied to this specific differential diagnosis. We performed a retrospective chart review of patients who underwent neuropsychological testing at the Geisel School of Medicine. The sample includes 114 patients diagnosed with ES and 33 patients diagnosed with PNES at the hospital's epilepsy monitoring unit. A series of independent t-tests will be performed to identify neuropsychological tests that discriminate the two groups. Tests with the largest effect size will be used as predictors in a logistic regression model to determine the best combination of test scores to discriminate between patients with ES and PNES. The equation will be made available to clinicians to guide test selection and provide an empirical estimate of the likelihood that a given seizure semiology has a psychogenic origin. If the psychometric testing produces clinically meaningful classification accuracy, it could serve as a valuable screening procedure or a confirmatory diagnostic tool in addition to biometric measures. Neuropsychological assessment is less invasive, more accessible and less expensive than in-patient video EEG monitoring.

1-G -233 Hanging Behavior in Mice is a Sensitive Marker of Animal Welfare

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Rodent welfare is typically determined from behaviors such as locomotion, exploration, sleep and feeding. However, these parameters are often insufficient to detect subtle declines in rodent welfare. Our preliminary experiments have revealed that cage-lid hanging behavior, which is identified by mice suspending themselves from the metal lid of their cage, serves as a novel and highly sensitive measure of mouse welfare. Using an automated video tracking system, we tested the hypothesis that hanging behavior correlates with pain and disease severity in mice. We observed that traditional animal models of acute (intraplantar capsaicin or formalin) and chronic pain (intraplantar complete Freund's adjuvant, Spared Nerve Injury) exhibited a drastic reduction in hanging behavior. In addition to standard pain models, which inflict pain by targeting the mouse paw and impede the ability of the mouse to hang, we observed that postsurgical pain (craniotomy), cancer pain and bladder cystitis pain (cyclophosphamide, i.p.) also decrease hanging behavior. Finally, we demonstrated that hanging behavior is also reduced by septic illness (lipopolysaccharide, i.p.). Interestingly, the effect of bladder cystitis pain and sepsis on hanging can be reversed using the analgesic, ketoprofen and the anti-inflammatory, indomethacin,

respectively. Collectively these results indicate that hanging behavior is a robust and sensitive readout of mouse welfare that can be easily incorporated to facilitate the early detection and resolution of pain or illness.

1-G -234 An Improved 3D Hydrogel Culture Model for Glial Scarring

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Implantable devices have been shown to have great potential to restore significant function in a range of injuries to the central nervous system; however, the innate immune response to implanted devices can reduce functionality and ultimately cause device failure. A glial scar composed of microglia and astrocytes eventually encompasses the electrode, partitioning the device from target neurons. Although remarkable improvements have been made to implantable devices and electrodes, in vivo testing remains an expensive and time consuming way to characterize biocompatibility. In our study we have developed an improved high throughput in vitro hydrogel model, encapsulating primary cultured glial cells, to enable study of the foreign body response to implanted devices. A 3D hydrogel was synthesized from methacrylated hyaluronic acid, via photo-crosslinking, to house the glial cells. The macromer concentration 0.5% w/v was used. Primary microglia and astrocytes were isolated from whole brains and cultured in mixed populations. 20% Geltrex, a basal lamina mixture, was incorporated to improve glial cell adhesion and mobility. Integration of microglia and astrocyte to the matrix was assessed by confocal microscopy. Morphology of the hydrogel was assessed with scanning electron microscopy. It was found the Geltrex enhanced cell integration with expansive glia networking, which was not present in the unmodified matrix. In summary, we have designed a 3D tissue-like system to test biocompatibility of implantable materials, which is tailored to the cells in a glial scar.

1-G -235 Automated Optogenetic and Mesoscopic Brain Imaging System for the Mouse Home-cage

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Over the last several years experiments that rely on awake and behaving mice have become a new standard. These experiments require the mouse to be head-fixed to obtain high quality optical data and is usually done chronically following many mice over the course of several weeks which can induce stress. Additionally these mice have to be trained to tolerate long sessions of head restraint, and since this is done for each mouse it can become a time consuming task for the experimenter. Here we describe a home-cage based system that automatically identifies, and head-fixes the mice while dispensing water rewards. The system is similar to the automated imaging system that we published before, but differs in its head-fixing mechanism and in the addition of a movable laser to stimulate different areas of the cortex while the mouse is head-fixed. The system can support up to ten mice that are automatically imaged, stimulated and weighed. We also describe a training protocol where the RFID identified mice learn to self-initiate brain imaging trials in order to obtain water rewards while their movement becomes progressively more restricted until they are fully head-fixed. The system utilizes the Raspberry Pi single board computer in order to minimize cost and thus maximize the potential to scale up the system.

1-G -236 A random-access, two-photon laser-scanning system design for comprehensive, in vivo and awake imaging of neural activity

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Understanding how neurons transform synaptic input and encode information in action potential firing output is a leading question in neuroscience. Neurons responding to sensory input allow tracking controlled responses of synapses and action potential firing to compare input/output. Neurons receive a variety of input tuned to distinct sensory stimuli, yet firing is often tuned to a restricted input-domain. How does a neuron respond to some inputs, but not others? What is the transformation of encoding at the level of synaptic input and action potential output? How are morphology, electrophysiological properties and synaptic integration related? Answers require simultaneously tracking all synaptic and firing activity in response to controlled sensory stimuli, in the intact and awake brain. Conventional microscopes lack temporal resolution to capture complete structural and functional activity, thus rates several orders of magnitude greater are required to capture the 4D data over sustained periods. We describe a random access, two-photon, laser scanning system capable of 'comprehensive imaging' of structural and functional activity of a neuron in an intact/awake brain. This system achieves Ca-imaging rate scanning using acoustic-optics to scan points-of-interest (POI) on neurons expressing Ca-sensitive fluorophores, allowing 3D analysis of all synaptic and firing activity including plasticity induced by external stimuli. Using POI-scanning we achieved rates orders of magnitude greater than conventional scanners to capture neuron state-representations over prolonged periods.

1-G -237 Fiber-optic imaging of FRET biosensors for recording GPCR signalling in vivo

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G protein-coupled receptors (GPCRs) mediate neuronal responses to neurotransmitters and neuromodulators, and are major drug targets in neuropsychiatric disease. Individual GPCRs signal via multiple downstream effectors, only some of which may mediate therapeutic effects in vivo. Furthermore, the specific complement of signalling cascades engaged by a given GPCR is determined by several factors, including the particular ligand, as well as the cellular and tissue context. Linking specific intracellular signalling events in defined cell populations to biologic effects in the whole animal would advance our understanding of GPCR function in disease states and facilitate the development of novel functionally selective ligands (i.e. those that only modulate a subset of pathways downstream of a given GPCR). We have developed a method for imaging Förster resonance energy transfer (FRET)-based biosensors that report signalling downstream of GPCRs in real time in live animals. We combine fiber-photometry-based fluorescent recording with genetically-encoded FRET biosensors that report GPCR-mediated second messenger production (cAMP, Ca2+) and protein kinase activity (PKA, ERK1/2) with high spatial and temporal resolution. Biosensors are expressed in wild-type animals using viral vectors and cell-type selective expression is achieved using specific promoters. Flexible fiber-optic patch cords allow imaging to be performed in freely moving animals, allowing the simultaneous measurement of behavioral and signalling responses to pharmacological manipulation.

1-G -238 Dynamic generation of thesaurus from text using deep learning

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This study aims to automatically generate a dictionary describing the grouping of words based on the semantic relations among them, that is, a thesaurus, from plain texts on the internet. A thesaurus used in natural language processing is always incomplete for making a system that behaves like a person, though usually requires a lot of expertise. Because language could change every day, the thesaurus

should be updated. As a first step of this study, we focused on only hypernyms, hyponyms and synonyms and attempted to construct classifiers. First, we made vector representations of wikipedia data in English using word2vec. Then, among the vectorized words, we extracted ones registered in wordnet, and determined one among the three relations. Finally, by deep learning, we trained multilayered neural network, whose input and output are vectors representations of any two words related each other and the relation, respectively. As a result, the discrimination rate has stayed at about 50 percent. In the future, the accuracy will be improved by using images as well as text.

H - History, Teaching, Public Awareness and Societal Impacts in Neuroscience

1-H -239 A Brain Museum Tour of Europe

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Europe has a rich history of neuroscience research and clinical neurology, but where can the history of European neuroscience be found? The historical artifacts, documents and discoveries of European neuroscience exist in many museums, but these are often forgotten or neglected within Europe and relatively unknown outside of Europe. The purpose of this project is to present a tour of the brain museums of Europe on a WEBSITE, showing the museums with materials relevant to the history of neuroscience in each country. The history of neuroscience relies of objects from the past and this website describes the collections related to brain research in European museums. Using this website will enable students and researchers to locate historical objects in museums and plan visits to these museums for teaching and research. The presentation will consist of a poster/oral presentation and a website which meeting participants can browse for information. The present poster/Website contains information on 31 brain museums in 18 countries, with more being added as we find them. The website is a work in progress and we hope that users will provide us with information about brain museums which we have not yet discovered. If you are planning a trip to one of the European cities with a brain museum, this website will guide you to the location and the exhibitions on view. Enjoy your tour of Brain Museums in Europe! This project is sponsored by the FENS History of Neuroscience Committee. If you know of brain museums not presented on this poster, please contact Richard Brown at rebrown@

1-H -240 Convergence, Perceptions of Neuroscience.

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Art in popular culture has a strong influence in shaping most people's understanding of science and scientists. Films, novels, comics, illustrations, and other media are usually more appealing, and more memorable than formal scientific lectures. The arts can be a strong tool allowing the public to situate and see themselves in the complexities of scientific inquiry. In 2014, the Council of Canadian Academies concluded that even when "Canadians have positive attitudes towards science" there is a need for evolution from a model focused on one-way communication from scientists to the public, to a two-way engagement model giving the public a voice throughout the scientific process (Science Culture 2014). A stronger science culture in Canada remains a work in progress. Convergence is the process by which two different elements merge into a unified whole. It is the spirit of the Convergence Initiative that in the last eleven months has placed together 16 neuroscientists on early steps of their careers from 12 different labs, plus 21 fine arts students of advanced cycles representing 14 different art disciplines.

Four major academic organizations, plus the efforts of dozens of volunteers and entrepreneurs joined in the common effort of changing perceptions in the students and institutions involved towards each other work. In the process, we have made neuroscience research more accessible to a general audience using the arts as media for communication. In this work, we present details of the project, the process, the methods, and the results of this experience.

1-H -241 The Multiple Roles Families Play, Including Unpaid Healthcare Providers, after Severe Brain Injury

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To capture the multiple roles family members of patients in a vegetative state (VS), minimally conscious state (MCS), or with locked-in syndrome (LIS) have while caring for a loved one we conducted semi-structured qualitative interviews with substitute decision-makers of individuals who have been diagnosed to be in a VS, MCS, or LIS. Using a constructive grounded theory design, family members were interviewed twice to capture the different roles they play, the relationship among these roles, and the burdens experienced. Twelve family members participated in the interviews for a total of 21 in-depth interviews to date. Family members described undertaking a wide variety of different roles including being a caregiver to the patient, caregiver to other family members, advocate, household provider, and financial and legal gatekeeper. Family members described in detail the physical, emotional, social and economic burdens experienced by them and the impact of these burdens on personal relationships and family dynamics. Family members caring for a loved one who has been diagnosed to be in a VS, MCS, or LIS undertake a variety of roles. Prominent among these is the role as unpaid health care provider, as families fill gaps in care that exist within the health care system. The complex relationship among the roles is a source of strain and burden for family members. Our findings suggest an urgent need to improve the support family members receive, including strategies to care for themselves.

IBRO International Brain Research Organization

1-IBRO-242 Prenatal stress induces vulnerability to nicotine addiction and alters D2 receptors? expression in the nucleus accumbens in adult rats

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Prenatal stress (PS) can induce several long-lasting behavioral and molecular abnormalities in rats. It can also be considered as a risk factor for many psychiatric diseases like schizophrenia, depression or PTSD and predispose to addiction. In this study, we investigated the effect of prenatal stress on the reinforcing properties of nicotine in the CPP paradigm. Then, we examined the mRNA expression of the D2 dopaminergic receptors using the quantitative real-time PCR technique in the nucleus accumbens (NAcc). We found that prenatally stressed rats exhibited a greater place preference for the nicotine-paired compartment than the control rats. Moreover, we observed an overexpression of the DRD2 gene in adult offspring stressed in utero and a downregulation in the PS NIC group (PS rats treated with nicotine) compared with their control counterparts (C NIC). These data suggest that maternal stress can permanently alter the offspring's addictive behavior and D2 receptors' expression.

1-IBRO-243 Promoting Oligodentrocytes Precursor cells proliferation and survival in Multiple Sclerosis

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Multiple sclerosis (MS) is a neurodegenerative disease at which demyelination of neurons happens. Microglia, lymphocytes, and macrophages are among the main reasons of such effect. Oligodendrocytes Precursor Cells (OPCs) are the main targets of inflammation and immune attacks which can cause their death by apoptosis; thus, not only demyelination occurs, but losing the ability of re-myelination is lost as well resulting in MS. In mice with introduced multiple sclerosis-like disease (active induction by immunization with myelin antigens), a combination of two drugs will be introduced integrating to positively affect OPCs proliferation and survival; consequently, a synergistic effect should be achieved. First, 'WIN55,212-2' chemical compound, with a cannabinoid-like effect, stimulates OPCs proliferation. It also has a neuroprotectant effect and induces oligodentrocytes maturation. Second, Minocycline, a lipophilic tetracycline antibiotic, that has anti-apoptic effect on oligodendrocytes. The drugs will be carried on a non-viral vector, a designed dendrimer will be used. Through stereotactic intra-cranial injection, the dendrimer including the nanosized drugs, will be injected. The experiment can be monitored by using TUNEL (Terminal deoxynucleotidyl transferase dUTP Nick End Labeling) to detect oligodentrocytes cells apoptosis level. Through the above steps and design, OPCs size and proliferation level should be enhanced and the reverse on apoptosis level, promoting control of the induced MS case and even an approach to make the case better.

1-IBRO-244 Light Sheet Fluorescence Microscopy (LSFM) as a tool to study the role of F-spondin in neural development of zebrafish

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Studying the mechanisms underlying both neural development and functioning in vivo is currently possible due to advances in light sheet fluorescence microscopy (LSFM). In our research, we use this technique to identify and characterize migration patterns in developing neurons expressing the extracellular matrix protein, F-spondin. F-spondin is a relatively novel protein which is highly expressed in the floor plate and has been proposed to play a role during embryonic morphogenesis and regeneration. It also contibutes to the development of the central nervous system (CNS) by accumulating in developing nerves, promoting neurite extension and precursor differentiation. We imaged Tg(spon1b:GFP) zebrafish embryos from 24 to 72 hours post-fertilization (hpf) and found two bilateral clusters of cells, one located at the anterior-ventral diencephalon, possibly the olfactory bulb primordium, and the other in the dorsal region. Given that the habenula is part of the dorsal diencephalic conduction system and connects the forebrain with the mid and hindbrain, we suggest that the second cluster could be the primordial of the ventral habenular nuclei. Performing 2D and 3D image processing we obtained single cell trajectories of optic tectum neurons, applying drift correction algorithms to account for shifts during development. Our results show that F-spondin expression can be identified in various regions of the CNS starting at early stages during embryonic morphogenesis, which is particularly useful to follow optic tectum development in vivo.

1-IBRO-245 Ten years of Canadian International Brain Research Organization (IBRO) Schools of Neuroscience

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Since its creation in 1961 by an act of the Canadian Parliament, IBRO has engaged in promotion of international collaborations amongst neuroscientists and in extensive educational programs directed primarily to students from countries in developing areas. Unlike the other IBRO schools of neuroscience, in which tutors travel to the students' countries, in the Canadian schools 10 - 14 students from Africa and Latin America are brought to Canada for a stay of 2-3 weeks. They are selected for their academic achievements and for their potential to change their environments. In the past ten years 125 students (70 women, 55 men) from 21 countries, ranging in age from 24-43 years (average 29.6 y) have attended the school. Most of attendees were graduate students (MSc: 9, PhD: 86), postdoctoral fellows (17) or junior faculty (13). Canadian IBRO Schools have unique features: students are not only taught through a series of interactive sessions by prominent Canadian neuroscientists but they also have an opportunity to visit various state-of-the-art laboratories, often gaining hands-on experience, and they attend and present a poster of their work at the Canadian Association for Neuroscience's annual meetings. The schools are supported by IBRO North American Regional Committee and several Canadian institutions.

Tuesday, May 30, 2017

A - Development

2-A -1 Translational control of neuronal subtype specification by the 4E-T repressive complex in neural precursor cells

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The diverse types of neurons that are organized into layers in the mammalian cortex are the fundamental requirement for the assembly of complex circuitry. However, the mechanisms regulating the genesis of these distinct neuronal populations from neural precursor cells (NPCs) are still not well understood. Here, we show that deep and superficial layer specific mRNAs are coexpressed in early NPCs during a period when only deep layer neurons are generated. We find that Brn1, which specifies superficial layer neurons, is robustly transcribed in early NPCs, but is not translated until later timepoints coincident with the genesis of superficial layer neurons. Interestingly, both deep and superficial layer specific mRNAs are associated with the translational repressor 4E-T, which we have previously shown is essential for neurogenesis (Yang et al., Neuron, 2014). To characterize these repressive complexes, we analyzed RBP-recognition motifs that are enriched in 4E-T bound mRNAs. This revealed several candidates, including Pumilio2 (Pum2), which interacted with 4E-T in NPCs. RIP-Chip analysis of both 4E-T and Pum2 shows that they coordinately regulate mRNAs encoding differentiation and specification-related proteins. Disruption of these complexes by knocking down either Pum2 or 4E-T leads to neuronal misspecification. Together, these results suggest that NPCs are transcriptionally primed to generate diverse types of neurons, but that a 4E-T-Pum2 complex represses translation of neuronal specifier mRNAs to determine the appropriate timing and identity of their daughter neurons.

2-A -2 Quaking deficient oligodendrocytes display major splicing defects of the key axoglial junction protein, Neurofascin-155, as well as self-splicing.

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Animal models of dysmyelination/demyelination play key roles in defining the biology of myelination and developing new treatments for Multiple Sclerosis. The Quaking (QKI) RNA binding proteins bind in a sequence-specific manner and regulate RNA processes including pre-mRNA splicing, mRNA export, translation and stability. We generated a conditional qkI null allele in mice (Darbelli et al., 2016, J. Neurosci 36:4106-20). Embryonic loss of QKI in OLs using Olig2-Cre resulted in extensive hypomyelination in the central nervous system due to loss of mature OLs, resulting in death at the third post-natal week. Adult loss of QKI using PLP-CreERT resulted in experimental autoimmune encephalomyelitis-like symptoms with hindlimb paralysis, immobility and death by 30 days post-tamoxifen injection. A transcriptomic analysis of qkI-deficient mice (Olig2-Cre) revealed major changes in gene expression and RNA processing with the top categories being axon ensheathment and myelination. Specifically, we identified a key axoglial junction protein in OLs (Neurofascin155) as the major deregulated alternative splice event leading to paranodal defects in these mice. In addition, we observed a switch in exon 2-deficient qkI mRNAs favoring the expression of qkI-5 rather than qkI-6 and qkI-7. These findings define the QKI proteins as master regulators of OL differentiation and demonstrate a requirement for their continuous expression in adulthood to maintain myelin and axoglial junctions integrity. This work was supported by the MS Society of Canada. L.D. is a recipient of a CIHR doctoral award.

2-A -3 Role of histone deacetylase 2 (HDAC2) in PV cell circuit development

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Cortical parvalbumin-positive basket cells (PV cells), the major source of GABAergic inhibition in the brain, innervate hundreds of postsynaptic targets with multiple synapses clustered around the cell body and proximal dendrites. These cells are particularly important for the regulation of many cognitive functions and developmental cortical plasticity. Although the function of PV cells is being explored extensively, the mechanisms that control their development and plasticity have not been entirely resolved. Molecular mechanisms involved in synapse formation and strengthening include the activation/repression of specific subsets of genes by stable epigenetic modifications. In particular, Histones Deacetylase 2 (HDAC2) has been shown to regulate excitatory synapse plasticity and memory formation. Whether HDAC2 affects PV cell synapse development is unknown. Here, we show that HDAC2 is expressed by PV neurons. To dissect the role of HDAC2 in PV cell development in vivo, we generated conditional KO mice (PV_Cre;HDAC2lox/lox), which express Cre selectively in PV cells after P14. We found that PV expression levels and PV cell perisomatic boutons density is significantly reduced in both the cortex and basal lateral amygdala by P60. Behaviorally, we found that adult PV_Cre;Hdac2lox/lox mice extinguish more efficiently fear memories than control littermates. We are now exploring the use of a specific Hdac2 inhibitor to erase fear memories. Our data imply suggest to modulate Hdac2 activity in combination with behavioral therapy for post-traumatic stress disorder (PTSD) treatment.

2-A -4 Characterization of cellular diversity in the embryonic cerebral cortex using single-cell genomics

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Corticogenesis, the assembly of the cerebral cortex during development, is accomplished by a population of radial glial cortical precursors (CPs) which are tasked with producing the three major cell

types of the cortex: neurons, astrocytes and oligodendrocytes. The processes by which CPs produce neurons and glia involve integration of a tightly controlled transcriptional program with information from the microenvironment. We recently identified a high level of complexity in the microenvironment of CPs and neurons during mid-gestation when predominately neurons are being produced based upon computational model predictions, smFISH and qRT-PCR. One possible explanation for this is that there may be pronounced heterogeneity within these cell populations in the embryonic cortex. To characterize cellular diversity and heterogeneity within the developing cortex, we have used high-throughput single-cell RNA-seq (scRNA-seq). Here we describe how we have deployed scRNA-seq at multiple embryonic time points during corticogenesis and identified the major cell types previously known to populate the cortex, and additionally, we reveal potential subpopulation heterogeneity within these cell types. We predict that identified subpopulations of CPs may play different roles in cortical development, producing different neuronal and glial subtypes. Since we have identified many potential ligands in the CP microenvironment, we are assembling a communication model between subpopulations of CPs and neurons that will enhance our understanding of how cells interact in the embryonic cortex.

2-A -5 Hoxb8:Cre represents spinofugal projections of nociceptive circuits

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Although unpleasant, nociception remains a vital aspect of maintaining our bodies. Primary afferents relay nociceptive signals from the periphery to spinal cord. This information is further processed at the spinal level and transmitted to higher brain regions. This system enables us to respond rapidly to noxious stimuli and provide a wide-range of appropriate behavioural responses. Nociception has been mostly studied at anatomical and physiological levels; to complement these experiments, we are characterising genetic labels of nociceptive projection neurons. The Hoxb8:Cre mouse line expresses Cre recombinase in the caudal dorsal root ganglia and spinal cord. Using an axonal Cre reporter, we have visualised Hoxb8:Cre spinal projections onto brain regions associated with nociceptive processing. These neurons innervate the parabrachial nucleus, periaqueductal gray, and thalamus. However, other nociceptive areas such as the amygdala and the septal nucleus are spared. We also began to study the developmental time course of Hoxb8:Cre projections noting that in newly born mice (P0), only some of the targets identified in the adult receive Hoxb8:Cre axons. Furthermore, we find that Hoxb8:Cre spinofugal neurons display differences in neurotransmitter identities. Our data provide highlight differences in the genetic identity of nociceptive spinal projection neurons. Moreover, our results identify Hoxb8:Cre as the first genetic handle of spinofugal neurons, allowing their anterograde labelling during early stages of development and as well as their functional analysis.

2-A -6 IL-6 and Its Receptor Are Required For the Maintenance Of Adult Neural Stem Cell Pools

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Neural stem cell pools that contribute to olfaction and cognition must last throughout the mammalian lifespan. The mechanisms that determine how these pools are maintained, however, are still largely unknown. Our laboratory reported that a transient maternal surge of interleukin-6 (IL-6) during embryogenesis resulted in long-lasting increases in the numbers of sub-ventricular zone (SVZ) neural precursor cells (NPCs) (Gallagher et al. Cell Stem Cell, 2013). We have now asked whether endogenous IL-6 and its receptor IL6Ra, which we show are both expressed in postnatal and adult NPCs, are important regulators of the maintenance of adult SVZ stem cell pools. We show that adult IL6-/- mice

exhibited an almost 50% decrease in adult SVZ neural stem cells. Moreover, when the IL6 receptor was inducibly deleted in adult SVZ neural precursors, this led to a significant depletion in the adult NPC pools. Since IL6 is a cytokine that is increased in the circulation in response to stress, infection, and neuropsychiatric disorders, we then asked whether increased circulating postnatal IL-6 would also influence stem cell pools. Injection of P7 mice with IL-6 resulted in a burst of SVZ NPC proliferation and a subsequent depletion of the NPC pools by P21. Initial experiments suggest similar decreases at 6-8 weeks. Collectively, these results identify an IL-6-dependent neural stem cell self-renewal and maintenance pathway in the adult, and support a model in which perturbations in this pathway may have long-lasting effects on stem cell pools and potentially cognitive outcomes in adults.

2-A-7 Structural connectivity abnormality in children treated for medulloblastoma

ADEOYE OYEFIADE[1], DONALD MABBOTT[1]
[1]The Hospital for Sick Children

Introduction. Treatments for medulloblastoma impart significant neurotoxicity on the brain. Though diffusion Tensor Imaging has been used to describe treatment-related changes to white matter, there remains a limited understanding of the effect of treatment on the dense, integrative network of connections present in the brain. We utilized a network analysis approach to characterize changes within a frontal network in a small sample of patients. Methods. Five medulloblastoma patients (13.9±3.4 yrs) and matched healthy subjects (13.9±3.6 yrs) were scanned at the Hospital for Sick Children. Transformed anatomical images were parcellated into pre-defined cortical areas after which connections between six bilateral frontal regions (superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus (triangular, operculum, orbital), precentral gyrus) were reconstructed. Network analysis was performed using the Network-based statitics Toolbox. Results and Discussion. NBS analysis ($p<0.05$) revealed no significant differences between patients and controls in structural network organization. However, we found a significant difference in nodal strength between both groups; [patients = 7.63±0.11, controls = 7.74±0.13; $p = 0.004$]. Further analyses revealed significantly lower average FA in right hemisphere connections of patients (p-values 0.06 - 0.007). Conclusion. Our results agree with prior studies showing increased vulnerability of right hemisphere connections to treatment and suggest preservation of network structure but deficits in connection strengths within networks.

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right hemisphere connections of patients (p-values 0.06 - 0.007). Conclusion. Our results agree with prior studies showing increased vulnerability of right hemisphere connections to treatment and suggest preservation of network structure but deficits in connection strengths within networks.

2-A -8 Early cannabis use initiation at 12-14 years old associated with thinner frontal and temporal cortical thickness

Flavie Laroque[1], Josiane Bourque[1], Sean Spinney[1], Rachel Sharkey[2], Travis Baker[3], Alain Dagher[2], Alan Evans[2], Hugh Garavan[4], Marco Leyton[2], Jean Séguin[1], Robert Pihl[2], Patricia Conrod[1]
[1]University of Montreal, [2]McGill University, [3]Rutgers University, [4]University of Vermont

The increase of cannabis (CAN) use among young Quebecers from 12% in 2008 to 15% in 2015 and its future legalization have intensified public health actions to fully understand CAN effects on brain. Thinner cortical thickness (CT) has been identified in adolescent using CAN but most studies focused on adolescent aged 15 and more. This investigation compares CT measures in early CAN users aged 12 to 14 years old compared to non-using controls. Eleven CAN users and 11 non-user adolescents (age 13.8±0.6, 7 females for each groups) were matched on age, gender, handedness, socio-economic status, IQ, alcohol use and personality. They underwent MRI anatomical scans and CT reconstruction was performed with two automated pipelines, CIVET 2.0 and Freesurfer. Region by region ANCOVA were conducted using SPSS with Freesurfer data. To confirm our results by a more restrictive approach, whole brain CT group differences were assessed using generalized linear mixed effects model in SurfStat. Both analysis were covaried for age, gender, handedness and intracranial volume. Compared to non-users, CAN users had significant thinner CT in temporal and frontal regions when assessing region by region analysis. Consistent with those results, whole brain analysis showed significant thinner CT in the left middle temporal gyrus of CAN users. To our knowledge this is the first study to evaluate CT in a group of early CAN user adolescents. Our findings are consistent with previous results in older adolescents and indicate that even at an early age of CAN use, brain abnormalities are observed.

2-A -9 Differential requirement for Kirrel-2 in the formation of the vomeronasal and olfactory glomerular maps.

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[1]McGill University

The encoding of information by sensory systems is dependent on the formation of continuous and discrete neural maps between sensory neurons in the periphery and second order neurons in the central nervous system (CNS). In regions of the nervous system where discrete maps are formed, such as the main and accessory olfactory systems, axons must converge or coalesce into distinct synaptic units. In these two systems, sensory neurons project axons that form synapses with second order neurons in neuropil structures termed glomeruli. Olfactory sensory neuron (OSN) axons coalescence into glomeruli on the surface of the olfactory bulb (OB), whereas vomeronasal sensory neuron (VSN) axons form glomeruli in the accessory olfactory bulb (AOB). The differential expression of cell adhesion molecules, such as members of the Kirrel family of proteins, on OSN and VSN axons has been proposed to play an important role in the accurate coalescence of these axons into glomeruli. Here, we have examined the role of Kirrels in the coalescence of axonal projections in both the OB and AOB through a loss of function approach. We show that ablating Kirrel2 and Kirrel3 expression leads to severe disruption in AOB glomeruli formation, which is associated with a decreased number of excitatory synapse in glomeruli. In contrast, loss of Kirrel-2 in OSNs only affects the coalescence of a small subset of OSN axonal populations. Our results indicate that Kirrels plays a prominent role in the coalescence of VSN axons but can be dispensable for the targeting of specific populations of OSN axons.

2-A -10 Calcium signaling determines the transition from quiescent to proliferative states of neural stem cell in the adult brain

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[1]Le Centre de recherche de l'Institut universitaire en santé mentale de Québec, [2]Helmholz Center Munich, Institute Stem Cell Research

Neural stem cells (NSC) persist in the subventricular zone of the adult brain and transit from the quiescent to the proliferative states to produce new neurons. The mechanisms regulating the transition from quiescent to proliferative states remain unclear. We used in vivo and ex vivo imaging approaches to selectively label, monitor and manipulate NSC activity. To label NSC, we electroporated CAG-GFP plasmid into the brain of newborn pups and analyzed GFP-retaining cells in the adult brain. Immunohistochemical characterization of label-retaining cells in the adult brain revealed that 49% of GFP+ cells are NSC. Continuous imaging of NSC in freely behaving animal for 3-4 days, revealed that lengths of cell division is 81 ±18.13 min. Since adult NSC are enriched in genes involved in the Ca2+ signaling, we next aim to determine whether the transition from the quiescent to the proliferative state is linked to changes in Ca2+ levels. We thus electroporated genetically encoded Ca2+ indicator GCaMP6s and performed Ca2+ imaging in GCaMP6s-retaining NSC at their quiescent and proliferative states. Our data revealed that quiescent NSC display 4-fold higher Ca2+ frequency as compared to proliferative NSC. We then employed pharmacological approach to dissect the mechanisms underlying different Ca2+ dynamics in NSC. Application of 2-APB, IP3 receptors antagonist showed a significant decrease in the frequency of Ca2+ events in quiescent NSC. Altogether, our data suggest that the mechanisms regulating the transition from quiescent to proliferative state are Ca2+-dependent.

2-A -11 mTOR pathway role during the development of cortical basket cell innervation is age-dependent

Clara Amegandjin[1], Mayukh Choudhury[2], Josianne Nunes Carrico[1], Graziella Di Cristo[1]
[1]Université de Montréal, [2]Mcgill

Cortical GABAergic Parvalbumin (PV)-positive basket cells (BCs) strongly regulate principal cell output and plasticity. The Mechanistic Target Of Rapamycin (mTOR) pathway has been implicated in controlling several aspects of neurodevelopment. Mutations in the regulatory components Tsc1 and Tsc2 of mTOR cause the disease Tuberous Sclerosis, which is characterized by seizures, mental retardation and autism. We investigate the role of mTOR activation in BC development. Tsc1 knockout in vitro caused a precocious increase in bouton density and terminal branching formed by mutant BCs. In vivo, at P18, Tg(Nkx2.1-Cre);Tsc1flox/flox mice showed both mTOR hyperactivation in BCs along with increased expression of PV in the perisomatic region of pyramidal neurons. In contrast, by P45, PV+-gephyrin+ perisomatic puncta density was significantly reduced. Study of BC axonal morphology in cultures from Tg(Nkx2.1-Cre);Tsc1flox/flox mice confirmed a faster rate of BC innervation maturation, followed at later stages by innervation loss. Additionally, Tg(Nkx2.1-Cre);Tsc1flox/flox mice exhibit Tsc1 dose-dependent increase in anxiety and deficits in working memory and social novelty behaviour. Tg(PV-Cre);Tsc1flox/flox mice showed a similar reduction of BC innervation at P45 accompanied by social novelty deficits. The reduction of BC innervation was confirmed by electron microscopy, which also revealed a reduction of synapses formed onto BC dendrites. All together, these results suggest that controlled mTOR activation regulates both the time course and the maintenance of BC innervation.

2-A -12 Presynaptic and Postsynaptic NMDARs in Refinement of the Developing Visual Circuit

Philip Kesner[1], Elodie Warren[1], Fan Ma[1], Edward Ruthazer[1]

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The N-methyl-D-aspartate type glutamate receptor (NMDAR) is essential to retinotectal refinement and plasticity during development. Although seminal studies of developmental axon remodeling utilized systemic receptor blockade, findings have generally been attributed to presumptive effects on postsynaptic NMDARs (postNMDARs). More recent experiments in other brain areas have revealed the existence of presynaptic NMDARs (preNMDARs) and suggested that they have roles in basal function and plasticity. In this light, we have begun to re-examine the respective contributions of preNMDARs and postNMDARs to brain circuit development. We have created a novel hemi-morphant model in which NMDARs are knocked-down in half of the developing Xenopus laevis albino tadpole by injecting an antisense Morpholino oligonucleotide (MO) against the GluN1 subunit of the NMDAR into one cell at the two-cell developmental stage. The utility of this approach lies in the fact that retinal ganglion cells (RGC) cross the midline to project to the optic tectum. Therefore, NMDARs are knocked-down in RGC inputs to their wildtype contralateral hemisphere (preNMDAR knockdown) and in all tectal neurons (sparing the RGC inputs) on the other side (postNMDAR knockdown). Using in vivo multiphoton imaging, electrophysiology, and immunohistochemistry we have begun to uncover unique roles for preNMDARs and postNMDARs in receptive field development as well as complementary contributions to axon complexity and dynamics, where preNMDARs appear to promote branch elaboration and postNMDARs mediate branch stabilization.

2-A -13 ProBDNF and mBDNF signaling underlie distinct activity-dependent processes in visual circuit development

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Sensory experience instructively refines topographic representations of the sensory world in the brain. Correlation in the firing of presynaptic inputs leads to the stabilization of synaptic contacts. Asynchronous firing of presynaptic inputs can lead to synaptic weakening and facilitates exploratory axon branching and growth, favoring the pruning and retargeting of inappropriate connections. Brain-derived neurotrophic factor (BDNF) is synthesized as precursor protein (proBDNF) and consequently cleaved to its mature form (mBDNF). Tissue plasminogen activator (tPA) and plasmin are believed to participate in the extracellular conversion of proBDNF to mBDNF. BDNF is a well-known modulator of synaptic efficacy with mBDNF signaling through TrkB to enhance synaptic strength and proBDNF working through p75NTR receptor to promote synaptic weakening. We used in vivo multiphoton imaging of retinal ganglion cell axonal growth in Xenopus laevis tadpoles, in conjunction with various visual stimulation paradigms to reveal the molecular mechanisms underlying synchrony-induced (Hebbian) stabilization and asynchrony-induced weakening of retinotectal inputs. TrkB-Fc injection to sequester endogenous BDNF prevents Hebbian stabilization of axonal branches. Presynaptic knock-down of p75NTR impairs both axon branch additions and eliminations. Blockade of tPA inhibits axonal branch elaboration over days. Our preliminary data suggest that proBDNF and mBDNF signaling may have opposing functions in asynchrony and synchrony-induced structural remodeling to encode proper circuit refinement.

2-A -14 The developmental program in differentiating neurons

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Gene expression is explicitly programmed in a spatiotemporal pattern and dynamically modulated throughout neuronal differentiation. While we are aware of critical genes in neurodevelopment, the integration of how, when, and where gene expression is turned on during human brain development has yet to be elucidated. To address this question, we are deleting eight genes that code for histone demethylases or histone methyltransferases that are associated with intellectual disability. Genes regulated by these histone modifiers are likely critical for brain development. Similarly, dysregulated genes common across two or more histone modifiers may point to necessary gene expression levels for normal development. For instance, a mutation in either KMT2D (lysine methyltransferase) or KDM6A (lysine demethylase) causes Kabuki Syndrome - a particular clustering of clinical features on the autism spectrum. This supports the idea that histone modifiers work together to regulate gene expression and that common mutations in different genes may lead to a similar phenotype. We will study this convergence using our method to rapidly produce induced pluripotent stem cells through simultaneous reprogramming and CRISPR/Cas9 gene editing to create isogenic heterozygous and homozygous knock-out models of histone modifier deficiency disorders and investigate their gene expression patterns using RNA-seq at three developmental stages (iPSC, NPC, mature neuron). Results from this study may identify a neurodevelopmental program that controls fundamental genes required for neurodevelopment in humans.

2-A -15 Stressed adolescent mice: The long-term effects of a short-term unpredictable stress on immunity

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Adolescence is one of the critical periods of development and have a great importance to health for an individual as an adult. Stressors have been shown to suppress immune function and increase susceptibility to inflammatory diseases. Thus, this study aimed to investigate the changes in sickness behavior, splenic T-lymphocytes subsets, NK cells and macrophages induced by LPS treatment employing a mouse stress model during adolescence. 30 days old Balb/c male mice were subjected to a random pattern of stressful situations twice daily for ten days. Twenty days after the end of the stress protocol, the animals were challenged by LPS. The sickness behavior was assessed by observed symptoms and 48 hours later, mice were euthanized and splenic cells and blood were collected for phenotypic analysis. The experiments were performed in accordance with the guidelines of the Bioethical Committee of FMVZ, USP, Brazil (no 4485180614). The sickness behavior assessment showed that stressed and challenged by LPS animals recovered more slowly than non-stressed and challenged by LPS group. Animals only stressed showed decreased in lymphocytes TCD8 and TCD4 subsets and animals stressed and challenged by LPS showed increased in macrophages and a decreased in macrophages MHC+ subset. In addition, there was a decrease of NK cells in all groups compared to the control group. Therefore, this unpredictable stress model causes long-term effects on immunity and appears to be a useful model in neuroimmunomodulation studies.

2-A -16 Refinement of silent synapses: A revision of the competition hypothesis

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During development, axons refine their connections by strengthening some inputs and eliminating others through a competitive process that relies on synaptic activity; in the absence of activity, refinement does not occur. While this hypothesis is generally accepted, the mechanisms that link activity to refinement remain largely unresolved. Recent work indicates that postsynaptic activity acts

on signaling pathways that reduce the action of 4E-BP, a repressor of cap-dependent translation. Therefore, we asked whether deleting 4E-BP to enhance translation could drive axons to refine in the absence of synaptic activity. To address this, we examined 2 mouse lines: One whose synapses in sympathetic ganglia are silent because of a deletion in the α3 nAChR subunit, and another in which 4E-BP has also been deleted (α3/4E-BP DKO). We used lipophilic dye tracing, immunostaining, electrophysiology, and viral-mediated gene transfer to examine the innervation of sympathetic neurons. In WT mice, preganglionic axons targeted their synapses to dendrites of sympathetic neurons and refined their innervation over the first postnatal month. Axons in α3 KO mice targeted silent synapses to the cell soma, and did not refine unless synaptic activity was restored. Surprisingly, when 4E-BP was deleted (α3/4E-BP DKO), preganglionic axons refined, even though synaptic activity was absent. Our findings indicate that the often cited competition hypothesis is incomplete. We demonstrate that synapses can refine in the absence of synaptic activity and identify 4E-BP as a critical player in this process.

2-A -17 Arp2/3 Complex Activation is Required for Commissural Axon Chemoattraction by Netrin-1

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Axons of the developing nervous system are steered to their final synaptic targets by guidance cues that line their path. Delivering attractive or repulsive signals, these guidance molecules direct the reorganization of the actin cytoskeleton that supports the sensory structure of the axon tip, known as the growth cone; thus directing motility of the extending axon. Netrin-1 is a well studied guidance cue that, when bound to the transmembrane receptor deleted in colorectal cancer (DCC), acts as an attractant for embryonic spinal commissural neurons. Binding to DCC initiates the formation of an intracellular signalling complex that includes Rho GTPases Cdc-42 and Rac1, as well as the nucleation promoting factor Neuronal Wiskott-Alrich Syndrome Protein (N-WASp). N-WASp binds both globular actin and the actin nucleating complex Arp2/3 which initiates the formation of new actin filament branches from existing filaments. The current study aims to establish the Arp2/3 complex as a downstream effector of netrin-1/DCC signalling for the re-organization of the actin cytoskeleton that underlies commissural axon guidance.

2-A -18 Long term effects of early life maternal deprivation and tyrosine receptor kinase B (TrkB) knockdown

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[1]Carleton University

Brain-derived neurotrophic factor (BDNF) signals through the tyrosine receptor kinase B (TrkB) receptor and has been implicated in stressor-related pathology, such as depression. Our work seeks to understand the developmental role of TrkB receptor signaling during infancy and in the context of stressor exposure. Indeed, little is known about how transient disruptions to TrkB signaling can influence the maturation of synapses, particularly during developmentally sensitive times. This is surprising given that early life stressors that can affect BDNF production are known predispose towards the later development of depression. Since constitutive TrkB knock-out mice do not survive past birth, we utilized a perfectly viable knock-in transgenic mouse line (F616A), with a mutation on the TrkB receptor, to reversibly block early postnatal BDNF/TrkB signaling. We also exposed a subset of these litters to early life maternal deprivation and then at 3 months exposed that subset to a chronic unpredictable stressor regimen to determine if the combined effects of TrKB knockdown and stress during infancy would influence stress resiliency in adulthood. The transient disruption of BDNF/TrkB signaling did indeed

appear to blunt the anhedonic responses provoked by the stressor exposures. Curiously, the F616A full knock-in mice also showed altered BDNF production and a trend towards a more anxious basal phenotype. These data are consistent with a role for early TrkB signaling in programming stressor responsivity.

2-A -19 Sema6d drives morphogenesis of the eye

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Background: During development tissues undergo morphogenesis to acquire their final functional shape. The eyes form from a region of the forebrain called the eye field, which splits into two eye vesicles that elongate after evaginating from the diencephalon, and then invaginate around the developing lens to form the optic cups. Time lapse imaging of eye specific fluorescent transgenic zebrafish has revealed the cellular events involved in optic cup formation. The molecular signals that drive morphogenesis, however, are poorly understood. Objective: Here we aim to identify a cell-cell contact mediated mechanism that functions in optic cup morphogenesis. Methods/Results: Using the zebrafish model, we find a member of the Semaphorin (Sema) axon guidance family of molecules, the transmembrane protein Sema6d, is expressed by progenitors of the early eye vesicle. Through antisense morpholino and CRISPR loss of function approaches we find that Sema6d acts through its receptor PlexinA1b to drive invagination of the eye vesicle around the lens. Gene marker analysis (tbx5, foxd1, epha4, vsx1, vax2, foxg1) and in vivo time lapse microscopy reveals that with the loss of Sema6d signalling progenitors of the medial leaflet of the eye vesicle are defective in their movement around the distal rim of the ventral optic cup. Conclusions: These data indicate that cell-cell contact mediated signalling between eye progenitors via Sema6d controls cell behaviours required for proper morphogenesis of the eye. Funding: Foundation Fighting Blindness

2-A -20 Early Exposure to TBECH Alters Motor Behavioural Outcome in Females

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The modification of the brain by experience, or brain plasticity, includes changes with both positive and negative experiences. Toxins in our everyday environments can lead to brain and behaviour changes. Of interest to us is 1,2-dibromo-4-(1,2-dibromomethyl)-cyclohexane (TBECH or DBE-DBCH), a fire retardant, as there is little evidence for its neurotoxicity. We hypothesized TBECH exposure during cerebellar development would impair motor coordination and motor skill learning. To examine the possible long term effect of neonatal exposure we used the rotarod and dowel walking tasks in juvenile and young adults, respectively. For the rotarod task, there was a significant effect of sex ($p < 0.01$, partial $\eta 2 = 0.293$), whereas the effect of TBECH was not significant. We tested the simple effects and found the females exposed to TBECH were driving the sex effect with much longer durations on later test days. The effect was not due to weight change in the TBECH animals, suggesting TBECH may have a sex-dependent effect on early motor coordination. For the dowel task and controls, there was a significant effect of sex ($p < 0 .001$, partial $\eta 2 = 0.607$), but no significant effect of TBECH. There was a significant effect of task ($p < 0.001$, partial $\eta 2 = 0.906$), but post hocs indicated no difference in running speeds within tasks. In this case, males were significantly slower, and heavier, but the effect did not interact with TBECH exposure. Our data suggests TBECH may impact male and female motor abilities differently during different developmental stages.

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

2-B -21 Cholinergic neurotransmission in different subregions of the substantia nigra differentially controls DA neuronal excitability and locomotion

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

2-B -22 Metabolic (de)coupling and interaction of glucose and lactate metabolites under varying systemic conditions

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Most textbooks highlight glucose as the main cerebral metabolic fuel. However, a competing hypothesis entitled the Astrocyte-to-Neuron-Lactate Shuttle hypothesis proposes that peripheral glucose, taken up by astrocytic end feet, can be converted to lactate and released in the extracellular space to be used by neurons as a source of metabolic fuel. Within this context, we examine the changes in lactate and glucose levels in the extracellular fluid of the motor cortex with the use of electrochemical electrodes as well as in tail vein blood following physiologically relevant intraperitoneal (i.p.) injections of glucose, fructose, galactose, lactate, pyruvate, β-hydroxybutyrate and insulin. Interestingly, i.p. injection of alternative fuels (i.e. glucose, fructose, lactate, pyruvate, β-hydroxybutyrate and, to a much lesser extent, galactose) all raised cortical extracellular glucose levels (200%). In contrast to the extracellular increase in glucose, all i.p. injections significantly raised blood lactate levels while cortical lactate levels remained largely unchanged. In summary, alternative metabolic fuels increase blood lactate while increasing cortical glucose. Though present methodology cannot infer causality (studies to follow) regarding the origin of the extracellular changes in glucose and lactate, these observations muse at the possibility that the extracellular cortical glucose increase is the product of circulating lactate. This, and other hypotheses, are further explored with these results and surrounding literature.

2-B -23 "Nanotrees" modulate synaptic plasticity

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Dendritic polyglycerol sulfates (dPGS) have been intensively studied because of their anti-inflammatory effects. Several studies suggested that interventions with small non-steroidal anti-inflammatory agents can be beneficial in early phases of neurodegenerative disorders involving neuroinflammation (e.g. Alzheimer disease). Neuroglia can contribute to the inflammatory processes, but they can also participate in the resolution of inflammation when not hyperactivated. Hypothesis: dPGS improves neural circuitry function by reducing direct toxic effects of Aβ species and lipopolysaccharide (LPS) and it normalizes hyperactivity of neuroglia. To test this hypothesis, primary enriched astrocytes, microglia and organotypic hippocampal slice cultures were treated with Aβ species or LPS in the presence or absence of dPGS. Electron microscopy, surface plasmon resonance, flow fractionation and atomic force microscopy were used to show the interactions between dPGS and Aβ species. Measurements from these studies suggest weak interactions between dPGS and Aβ and dPGS-driven propagation of Aβ fibril formation. dPGS are avidly taken up by microglia and astrocytes in a concentration and time dependent manner. Also, LPS and Aβ induce lipocalin 2 expression in astrocytes and significantly reduce a number of dendritic spines in hippocampal organotypic cultures. dPGS normalize hyperactive neuroglia and reduce synthesis and release of cytokines and lcn-2. Conclusion: dPGS mechanisms of action include direct interactions with Aβ species and normalization of hyperactive neuroglia.

2-B -24 L-type voltage gated calcium channels functionally couple with IKCa channels in CA1 pyramidal cells to generate the slow afterhyperpolarization

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The current work examined the extent to which the properties of Cav1 L type calcium channels are imparted on KCa3.1 channels believed to be involved in generating a slow afterhyperpolarization (sAHP). Coexpression of CaV1 and KCa3.1 cDNA in tsA-201 cells revealed that either CaV1.2 or CaV1.3 is sufficient to activate KCa3.1 channels, with a close relationship between voltage-dependent activation of CaV1 currents and the magnitude of KCa3.1. Moreover, step commands that maximally activated CaV1 channel isoforms for 5-150 msec produced a graded activation of KCa3.1 that lasted 1-5 sec, effectively recreating an IsAHP. Recordings from CA1 pyramidal cells in vitro in the presence of blockers against all CaV channel isoforms (except L-type) confirmed the activation of IsAHP that was sensitive to 1 µM TRAM-34. Similarly, application of 500 nM isradipine determined in tsA-201 cells to block CaV1 but not KCa3.1 channels reduced IsAHP area and spike accommodation in CA1 pyramidal cells. Moreover, CaV1.3 but not CaV1.2 channels exhibited calcium-dependent facilitation when coexpressed with the scaffolding protein densin and CaMKII. Further, siRNAs against densin reduced IsAHP area and calcium-dependent facilitation in cultured hippocampal pyramidal neurons. The CaV1-mediated activation of IKCa channels was blocked by internal 5 mM EGTA, suggesting a microdomain-interaction. The results suggest that L-type calcium channel isoforms, and more specifically CaV1.3, are sufficient to activate KCa3.1 channels in a manner consistent with the sAHP in CA1 pyramidal neurons.

2-B -25 Using Computational Modeling to Estimate Synaptic Receptor Densities Along Hippocampal CA1 Interneuron Specific 3 Cell Dendrites

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The inputs to any given cell type will dictate its in vivo roles, such as inputs that occur during behavior-associated network rhythms. It is therefore important to characterize the types of inputs that different

cell types receive. Here we focus on computationally predicting the properties of inputs along the dendrites of interneuron specific-3 (IS3) cells in CA1 hippocampus. Using experimentally-obtained excitatory and inhibitory postsynaptic currents (EPSCs and IPSCs), we optimize the synaptic parameter values for each compartment in a passive morphologically detailed IS3 cell multi-compartment model, such that the model successfully replicates the data. We obtain conductance values for single AMPA and GABAA receptors from the literature, which, together with our optimized synaptic weight values, could allow estimating ranges of AMPA and GABAA receptors per synapse with distance from soma. Our simulations showed that the estimates of receptor number per synapse are larger than could be expected, given the maximal numbers of receptors per synapse found in other cell types. To rectify this over-estimate, we established a simplified linear synaptic weight rule with distance from soma based on the weight values obtained from the most optimal fits. With the results obtained, we predict higher estimates of synaptic receptor densities in IS3 cell distal dendrites. Moving forward, these estimates of weight values along IS3 cell dendrites will contribute towards simulating in vivo-like activity patterns with our IS3 cell model.

2-B -26 A rat versus mouse comparison of microglia in different activation states: molecular profiles, K+ channels and migration

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Microglia help maintain homeostasis in the healthy brain, but also respond rapidly to perturbations adopting a reactive phenotype. Microglial activation is modeled after macrophage responses in vitro, with two extremes being pro-inflammatory (M1), which is thought to exacerbate tissue damage, and multiple anti-inflammatory (M2) states, which are thought to mediate tissue repair and inflammation resolution. Presently, we do not know whether rat and mouse microglia share the same activation phenotypes. The objective of this study was to quantify molecular responses and functional consequences of M1 (stimulated with interferon-γ + tumor necrosis factor-α [I+T]) and M2 (stimulated with either interleukin [IL]-4 or IL-10) activation of primary rat (Sprague-Dawley) and mouse (C57BL/6) microglia, and address the potential of targeting two K+ channels (Kir2.1, Kv1.3) to control their activation. Cell morphology, expression profile, activity of Kir2.1 and Kv1.3, and the involvement of these channels in microglial migration, proliferation, and nitric oxide (NO) production were assessed. Some responses were similar for both species; e.g., I+T induced NO production and reduced their migration, while IL-4 and IL-10 increased their migration. However, several responses differed; i.e., morphological changes, inflammatory expression profiles, K+ channel activity. We conclude that the rodent species can affect the outcome of microglial activation and should be further compared in pre-clinical in vivo studies.

2-B -27 Crosstalk Between the Immune and Nervous Systems: How peripheral inflammation can predispose the brain to hyperexcitability

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Recent studies suggest that peripheral blood mononuclear cells (PBMCs) infiltration into the brain following immune response contributes to epileptogenesis. However, the influence of PBMC extravasation on neural function remains elusive. Therefore, we developed an in vitro model to mimic PBMC infiltration into the brain, which consists of organotypic brain cultures (OTCs) comprised of the hippocampus (Hp) and overlying cortex (Cx) derived from P9 rats, co-cultured with PBMCs harvested from the spleen of the same rat. PBMCs are first incubated overnight with the immunogens

lipopolysaccharide (LPS) and Nigericin (NIG) to trigger inflammation before being seeded on the Cx of OTCs. Whole-cell recordings showed that in OTCs co-cultured with LPS+NIG activated PBMCs, pyramidal neurons of both the Cx and Hp manifested enhanced hyperexcitability compared to naive OTCs. Furthermore, pro-inflammatory markers, like NLRP-3, were elevated in hippocampal and cortical astrocytes of these slices, thereby implicating astrocytes in inducing neuroinflammation. Strikingly, in OTCs co-cultured with PBMCs treated with LPS only, hyperexcitability and astrogliosis were exclusive to the Hp, whereas the Cx seems to be comparable to naive OTCs, in spite of PBMCs being deposited over the Cx, thus, suggesting higher susceptibility of the Hp to inflammation versus the Cx. Hence, PBMC infiltration appears to elicit pro-excitatory neuronal changes induced by inflammation-activated astrocytic mechanisms, which could be reversed by blocking pro-inflammatory cytokine pathways, e.g. Interleukin-1 signaling.

2-B -28 Differential Effects of Local Aromatase Inhibition on Hippocampal Theta Oscillations in Male and Female Rats

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Hippocampal neurons in both male and female rats produce and respond to the estrogenic hormone 17β-estradiol (E2). E2 rapidly affects hippocampal synaptic activity and plasticity, and contributes to learning and memory. Hippocampal theta activity (4-14 Hz), a prominent oscillatory pattern detectable the hippocampal formation and entorhinal cortex, is thought to be involved in synaptic plasticity and hippocampal-dependent memory processes. Surprisingly, to date, the potential function of locally synthesized E2 in influencing theta generation in the hippocampus has not been investigated. Here, we examined the effects of reducing local E2 synthesis in the CA1 field by local application of the aromatase inhibitor fadrozole (FAD) on theta activity elicited by electrical brainstem stimulation in adult, urethane-anesthetized rats. In the presence of artificial cerebral spinal fluid, both the frequency and power of evoked theta remained stable for 3.5 hours. In males, hippocampal FAD application significantly reduced theta power without altering theta frequency. In contrast, FAD application did not alter hippocampal theta activity in females. Together, these data suggest that locally synthesized E2 is a potent regulator of hippocampal theta activity in male, but not female, rats. Ongoing experiments investigate the sensitivity of theta to local aromatase inhibition as a function of gonadal E2 levels and explore the consequences of E2-mediated modulation of hippocampal theta oscillations in learning tasks involving hippocampal circuitry (supported by NSERC).

2-B -29 The NDR kinase Lats1 controls hippocampal dendritic spine development through the scaffolding protein Angiomotin

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Angiomotin (AMOT-130) and the Hippo pathway kinases Lats1/2 are critical for epithelial tissue organization but almost nothing is known about their roles in the central nervous system (CNS). To address the role of AMOT-130 in the CNS, using biochemical and optical techniques in dissociated primary hippocampal neurons, we report that AMOT-130 is recruited into dendritic spines. The spine localization is dependent on the N-terminal region of AMOT-130, while the carboxyl-terminal PDZ binding motif is necessary for its association with post-synaptic proteins including PSD-95 and MUPP1. We further identified a novel role for Lats1 and AMOT-130 in regulating dendritic spine maturation. We find that the serine threonine kinase Lats1 specifically phosphorylates a conserved serine residue (S-175) in the N-terminal region of AMOT-130. This phosphorylation leads to the exclusion of AMOT-130 from

dendritic spines at the onset of spine development. During the first week of postnatal development reduced Lats1 activity corresponds with increased AMOT-130 expression and a concomitant decrease in AMOT-130 phosphorylation, stabilization of actin filaments and synaptic maturation. Reduction of AMOT-130 protein, compromises actin dynamics, and reduces the clustering of postsynaptic scaffolds as well as the presynaptic marker Bassoon. This is mirrored by excessive spine growth. In conclusion, these findings identify AMOT-130 as a novel regulator of developing synapses and uncover a link to the NDR kinase Lats1 in this process.

2-B -30 Isolating the Bulk Endosome from Nerve Terminals

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In neuronal synapses activity dependent bulk endocytosis (ADBE) is triggered by high activity to recover large amounts of internal membrane that fused with the plasma membrane. Key regulatory mechanisms and cargo proteins have been identified using targeted approaches, yet mechanisms that regulate formation and the fate of bulk endosomes (BEs) remain unknown. Our aim is to identify the proteins localised to BEs as a first step to understand ADBE regulation and we developed a method to separate BEs from synaptic vesicles (SVs) for mass spectrometry (MS) analysis. Methods: Percoll synaptosomes from whole rat brains were treated with control or high K+ stimulation, at a level to enrich for BEs, in the presence of a fluid phase uptake marker (horseradish peroxidase (HRP)). Organelles from lysed synaptosomes were separated on a density gradient. Proteins from each fraction were analysed by western blot and quantitative MS: TMT 10-plex of select fractions down a control gradient analysed by localisation of organelle proteins by isotope tagging (hyperLOPIT), or dimethyl-labelled fractions between control and high K+ gradients. Organelles from combined density fractions of high K+ gradients were studied by electron microscopy (EM). Results: Two populations of BEs are proposed based on overall protein and HRP changes down the gradient. EM images confirm the presence of large HRP labelled structures in putative BE regions. HyperLOPIT-defined clusters indicate the organelles involved in BE formation, and pathway analysis supports a role for WASP/WAVE actin regulation in BE formation.

2-B -31 Neural synchronization through electric field effects

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The ionic currents underlying an action potential generate an electric field. This electric field will induce an electrical potential (voltage) in the extracellular space, which can influence the transmembrane potential of another nearby neuron. This effectively couples the two neurons without any form of synaptic contact. Commonly referred to as ephaptic coupling, this electric field effect is nonspecific and diffuse, which in contrast to traditional synaptic coupling is poorly understood. To address this, we created a novel, computational approach for modeling ephaptic coupling. We use this approach to study synchronization and phase locking in small (2-3) model neuron networks. We found that synchronization and phase locking was robust in these small networks, but the number of stable states was greater than what is typically seen with similar networks involving synaptic coupling. Synchrony in neural networks is of interest in many contexts, from pathologies (e.g. epilepsy) to learning and memory; our results suggest that ephaptic coupling adds richness to such dynamics and may be involved in their generation and control.

2-B -32 Voltage-gated sodium channel isoform Nav1.5 contributes to Purkinje neuron firing.
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Voltage-gated sodium channels exist in nine isoforms (Nav1.1-1.9), and are major determinants of cell excitability. They have been found to be expressed in several electrically active tissues such as the nervous system, the heart, the skeletal muscles, or the digestive tract. In neurons of the central nervous system, Nav1.1, Nav1.2, Nav1.3, and Nav1.6 isoforms give rise to the upstroke of the action potential (AP), and are characterized by their nanomolar sensitivity to tetrodotoxin (TTX) block. Previous studies have also reported "heart-specific" TTX-resistant Nav1.5 isoform transcripts in the rodent and human brain (Donahue et al., 2000). The detailed location and role of Nav1.5 in the brain is unknown. Using RT-PCR, we detected Nav1.5 mRNA from mouse cerebellar extracts as two splice-variants - Nav1.5a and Nav1.5e - suggesting that Nav1.5 in the cerebellum adopts the form of Nav1.5ae. Heterologous expression and electrophysiological characterization of Nav1.5ae revealed a ~10 mV depolarizing shift in the activation profile when compared to the cardiac variant. Immunolabeling revealed Nav1.5 to be expressed in the dendrites and somata of Purkinje neurons. Whole-cell recordings in acute cerebellar slices showed that blocking Nav1.5 with the antiarrhythmic ranolazine significantly reduced the firing response of Purkinje neurons to step depolarization, without altering AP threshold. Our data establish the expression of Nav1.5 in Purkinje neurons, and suggest its important role in cerebellar physiology.

2-B -33 Balance of excitability is an epileptogenesis factor in traumatized mice
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Brain trauma in some patients leads to epilepsy. The mechanisms of epileptogenegis are unknown. We hypothesized that brain damage leads to partial deafferentation and a drop in excitability of the affected area. To compensate, the brain employs a variety of mechanisms to restore this drop of excitability and if not properly controlled, this leads to epilepsy. In order to induce seizure in adult C57/BL6 mice we performed undercut in the somatosensory area to reduce network excitability. In the following weeks all adult mice became epileptic. We manipulated the excitability of the network by applying DREADD technology. Target cortical regions were injected with AAV-hM3D(Gq) or AAV-hM4D(Gi) with different concentrations. The designed receptors were activated by clozapine-N-oxide continuously injected via an osmotic pump. Activation of hM3D(Gq) leads to depolarization and increased firing in infected neurons, while the activation of hM4D(Gi) induces a hyperpolarization of neurons. Mice in which hM4D(Gi) was activated revealed earlier and more severe seizures. The mice that had moderate amount of neurons infected with hM3D(Gq) showed either abolition or strong reduction of epileptogenesis suggesting this increase in excitability could compensate the drop in excitability induced by undercut. Expressing hM3D(Gq) in huge amount of cortical neurons in undercut mice lead to over-excitability of the network and epilepsy. These results demonstrate that manipulation of excitability can alter course of epileptogenesis. Supported by CIHR and NSERC

2-B -34 Astrocyte Resting Calcium Decrease via Bicarbonate due to External K+ Elevation
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Astrocytes rely on changes in free intracellular Ca2+ to regulate neuronal function via their fine processes that wrap synapses, as well as to regulate the blood supply through their endfoot processes that appose blood vessels. Elevations in external [K+], occurring from increases in neuronal action

potential signaling, is sensed by astrocytes to aid in K+ homeostasis; however, whether physiologically relevant changes in external K+ can link to changes in astrocyte free Ca2+, with an impact on astrocyte functions remain poorly defined. Using a two-dye, ratio-metric imaging approach with two-photon fluorescence microscopy, we examined the resting free [Ca2+] in astrocytes in response to bath application of isosmotic high K+ solution. We found that an elevation in external K+ from 2.5 mM (to 3.5, 5 or 7.5mM) caused a significant decrease in astrocyte Ca2+ in a dose dependent manner. The astrocyte Ca2+ decrease lasted only for the K+ application and fully recovered to baseline after 20 minutes of washout. This effect persisted in the presence of TTX. Blocking select pathways for K+ and Ca2+ movement, such as SERCA pumps and inward rectifier K+ channels, did not impact external K+ induced astrocyte Ca2+ decrease. Replacing bicarbonate with HEPES in the ACSF completely prevented the external K+ induced astrocyte Ca2+ decrease. Our data demonstrate a previously unrecognized phenomenon in astrocytes. We speculate that this cell-wide change to the resting cytosolic [Ca2+] will impact Ca2+-dependent astrocyte control pathways in the regulation of synapses and vasculature.

2-B -35 Effects of Endogenous Neuropeptides in the Bed Nucleus Stria Terminalis and Changes in Chronic Stress-Induced Anxiety-Like Behaviour

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Chronic stress is a major cause of anxiety disorders that can be reliably modeled pre-clinically. Stress-mediated deregulation of the bed nucleus of the stria terminalis (BNST) is strongly associated with anxiety-like behaviours. We hypothesized that chronic stress alters neuropeptidergic modulation of BNST synaptic transmission that can precipitate anxiety disorders. Uncovering these changes may provide much needed insight into alternative therapeutic targets for this mental health illness. We use brain slice neurophysiology and behavioural pharmacology to compare the role of locally released neuropeptides on synaptic transmission in the oval (ov) BNST of non-stressed (NS) or chronic unpredictably stressed (CUS) rats. We found that post-synaptic depolarization induced the release of vesicular neurotensin (NT) and corticotrophin releasing factor (CRF) which co-acted to increase ovBNST inhibitory synaptic transmission in 59% of recorded neurons. CUS bolstered this potentiation (100% of recorded neurons) through an enhanced contribution of NT over CRF. In contrast, locally-released opioid neuropeptides decreased ovBNST excitatory synaptic transmission regardless of stress. Consistent with CUS-induced enhanced contribution of the modulatory effects of NT, blockade of ovBNST neurotensin receptor 1 and 2 (NTR1/2) completely abolished stress-induced anxiety-like behaviours in the elevated plus maze paradigm. Our data highlights NT as a key link of chronic stress-induced anxiety behaviours. This is a novel finding as up until now, NT has been largely overlooked.

2-B -36 Dual imaging of neuron and astrocyte calcium signals in vivo with genetically encoded calcium indicators

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Localized, heterogeneous calcium transients occur throughout astrocytes, but the characteristics of these signals and how they correlate with neuronal activity, particularly in response to sensory stimulation, remain unknown. We investigated astrocyte calcium signals within the active cortical circuit by dual labelling mouse astrocytes and neurons with genetically encoded calcium indicators, GCaMP6s and RCaMP1.07. Images of calcium signals were acquired from awake mice via two-photon laser scanning microscopy through a chronic cranial window during periods of single-whisker deflection.

Regions of interest and signal peaks from both cell types were identified from the images using an activity-based, MATLAB analysis. Simultaneous visualization of both cell types permitted association of neuronal and astrocyte signals in time and space during sensory-evoked and spontaneous activity. This work provides new insight into the characteristics of intracellular astrocyte calcium signalling within active cortical circuits, and similar methods could be used to study astrocyte-neuron interactions in other pathways.

2-B -37 Action Potential-Induced Calcium Responses Actively Backpropagate in Spinal Cord Lamina I Neurons

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Spinal cord lamina I neurons function as a hub of nociception, and exhibit hyperexcitability in chronic pain models. Voltage-gated calcium channels (VGCCs) have been implicated in chronic pain, however their functionality in lamina I neurons is poorly understood. Here, we measured activity-driven calcium responses in lamina I neurons using simultaneous two-photon calcium imaging and electrophysiology. We made current-clamp recordings from lamina I neurons in spinal cord slices, loading the calcium indicator OGB-1 and control fluorophore AF-594 via the patch pipette. Neuronal calcium levels before, during, and after action potential (AP) generation were quantified as ΔG/R (change in OGB-1 intensity as compared to AF-594). Recordings were made from over 150 lamina I neurons. In 98% of neurons a single AP was sufficient to increase ΔG/R in the somatic cytosol (ΔG/R=0.11, n=157 cells), nucleus (ΔG/R=0.049, n=157 cells), dendrites (ΔG/R=0.16, n=157 cells), and dendritic spines (ΔG/R=0.089, n=19 spines). These calcium responses were ablated by the VGCC blocker cadmium. Responses didn't degrade along dendrites from 20µm (ΔG/R=0.10, n=6 dendrites) to 160µm (ΔG/R=0.13, n=6 dendrites) away from the soma, indicating dependence on VGCCs and active backpropagation. We found no differences when grouping calcium responses by cellular morphology or firing-type. Our findings suggest that all lamina I neurons produce AP-induced calcium responses that backpropagate actively into their dendritic arbour, which has been shown in other neuronal cell types to increase cellular excitability.

2-B -38 Astrocytes impose a pathway-specific control over synaptic strength diversity in the hippocampus

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Astrocytes have emerged as key regulators of neural circuit function, in part via their influence at individual synapses. Hippocampal astrocytes have the potential to both strengthen and weaken basal synaptic transmission, but whether and how these two opposing forms of strength regulation interact across populations of synapses is unknown. To begin to examine this issue we used paired pulse ratios (PPRs) to estimate the strength of multiple presynaptic terminals that converge onto single CA1 neurons in acute hippocampal slices of adult mice. PPRs measured at two independent inputs within the stratum radiatum (SR) were found to be highly heterogeneous under control conditions. However, in the presence of NMDA receptor antagonists, PPRs became significantly more similar, even when MK801 was included in the patch pipette. This PPR normalization was due to the strengthening of some synapses and the weakening of others. Knockdown of the obligate NMDA receptor subunit, NR1, specifically from GFAP-positive astrocytes led to a similar reduction in PPR disparity across SR synapses. PPRs recorded in response to the stimulation of multiple stratum lacunosum moleculare (SLM) inputs did not demonstrate a similar sensitivity to NMDA receptor antagonism or astrocyte-specific NR1 knockdown. Simultaneous recordings from astrocytes located in the SLM and SR reveal different responses to bath-

applied NMDA. Our findings suggest that astrocytes initiate pathway-specific signaling via NMDA receptors to maintain a diversity of presynaptic strengths in the hippocampus.

2-B -39 Plasticity of miniature synaptic transmission revealed by optical imaging of Ca2+ transients in cultured hippocampal neurons.

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Miniature synaptic transmission has been shown to have a functional role in the regulation of synaptic plasticity. Historically synaptic plasticity has been studied using electrophysiology, which reports on a large fraction of inputs on the neuron, with no spatial information. Since the extent of plasticity and the underlying mechanisms are likely to vary across the multiple synaptic inputs that neurons receive, we need to use methods that can monitor the plasticity of identified synapses. We are using wide-field optical imaging of a genetically-encoded Ca2+- sensor GCaMP6f to record miniature synaptic Ca2+-transients in cultured hippocampal neurons. These miniature synaptic Ca2+-transients are mainly mediated by NMDA receptors, as they are blocked by APV. Following a brief chemical stimulation (0Mg2+/Glycine/Bicuculline), our observations indicate a synapse-specific plasticity of spontaneous transmission expressed as i) an increase in the number of synapses per neuron exhibiting miniature Ca2+ transients and increased ii) frequency and iii) amplitude of miniature Ca2+ transients per synapse. We are investigating the mechanisms supporting this plasticity, which may have pre- and postsynaptic contributions. Our findings suggest that it is dependent on NMDA receptor subunit GluN2B, and protein kinase A, but not Ca2+/calmodulin kinase activity. We also aim to use this approach to investigate homeostatic plasticity mechanisms. Monitoring selectively potentiated synapses should allow us to further understand the diversity of molecular mechanisms that support synaptic plasticity.

2-B -40 AMPAR auxiliary proteins relieve channel block by facilitating polyamine permeation

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Many cation-selective ion channels exhibit inward rectification, a phenomenon attributed to the voltage-dependent block by intracellular polyamines. For non-NMDAR ionotropic glutamate receptors (iGluRs), polyamines have been well-characterized to act as permeant channel blockers. However, an increasing number of studies demonstrate that synaptic iGluRs associate with auxiliary proteins, and that these interactions effectively reduce polyamine block. Although the mechanisms underlying this relief of channel block remain unclear, it was recently shown that the KAR auxiliary proteins, Neto1 and Neto2, attenuate polyamine block by enhancing blocker permeation through the channel pore. Here, we show that the auxiliary proteins of AMPARs, gamma2 and CNIH-3, also facilitate polyamine permeation through the channel. Using a new model of channel block that includes a polyamine conductance, we propose that high polyamine permeation hinders Na+ permeation, causing a reduction in the overall channel conductance especially at positive membrane potentials. Although the exact structural mechanism remains to be investigated, our study provides insight into a functional mechanism underlying the relief of polyamine block that is shared among the auxiliary proteins of iGluRs, and that could also apply to other cation-selective ion channels. Furthermore, given the unexpectedly high levels of polyamine permeation, AMPARs with auxiliary proteins could be used by cells to regulate intracellular polyamine levels.

2-B -41 Understanding the structural basis of slow NMDA receptor gating

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Signalling at glutamatergic synapses is characterized by rapid and slow gating behavior of AMPA and NMDA receptors, respectively. Although rapid AMPAR gating has been linked to the apex of the ligand-binding domain (LBD) dimer interface, a comparable analysis of NMDARs is still lacking. Here, we identify a distinct contribution of the hinge region of the LBD dimer interface to NMDAR gating. Accordingly, channel opening is governed by interactions unique to the hinge region. Positive allosteric modulators (PAMs) occupy the hinge site and therefore our data propose they enhance the NMDAR response by hijacking the role of endogenous dimer interface residues. Finally, since these contact points are shared by all GluN1/GluN2 NMDAR isoforms, our findings establish the importance of the LBD dimer interface in dictating the default gating behavior of NMDARs.

2-B -42 Characterization of synaptic proteins expressed in dopaminergic axonal terminals
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Dopamine (DA) neurons of the substantia nigra compacta (SNc) and ventral tegmental area (VTA) establish a complex axonal arborization comprising axon terminals that are either synaptic or non-synaptic in structure, as revealed by ultrastructural observations. No method other than electron microscopy has previously been used to examine the synaptic or non-synaptic nature of DAergic axonal varicosities. Our objective was to develop a rapid and efficient in vitro method for analysis of synaptic and non-synaptic terminals in DA neurons. Considering previous works showing that DA neurons are able to release glutamate or GABA as some of their terminals, we took advantage of well-established postsynaptic markers of such synapses (PSD95 and gephyrin), to characterize their axonal domain. Primary DA neurons were prepared from the SNc or VTA of tyrosine hydroxylase (TH)-GFP transgenic mice and placed in co-culture with striatal neurons. Immunocytochemistry and confocal microscopy were used to examine the colocalization of the pre and postsynaptic markers. Our results show that the majority of axon terminals established by DA neurons contain the presynaptic markers synaptotagmin 1. However, only a minority were found to be associated with PSD95 or gephyrin. Furthermore, by evaluating uptake and release of the activity-dependant probe FM1-43, we found that the majority of axonal varicosities established by DA neurons are physiologically active. Our results validate the establishment of strategy to quantify the proportion of synaptic and non-synaptic contacts established by DA neurons.

2-B -43 Non-canonical cAMP-dependent synaptic potentiation in the paraventricular nucleus of the hypothalamus
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The activation of the hypothalamic-pituitary-adrenal (HPA) axis--a hallmark of the stress response--relies on the release of corticotropin releasing hormone (CRH) from neuroendocrine neurons in the paraventricular nucleus of the hypothalamus (PVN). The activity of these PVN-CRH neurons is controlled by neuromodulators, many of which act through cAMP. The crosstalk between synaptic transmission and neuromodulators is a brain wide principle for fine-tuning and plasticity of behavioural output, but little is known about how these mechanisms operate at the HPA axis output neurons. By using patch

clamp electrophysiology in ex vivo mice brain slices, here we report that forskolin (an activator of cAMP signalling) potently stimulates glutamatergic transmission onto PVN-CRH neurons, and that this cAMP-mediated synaptic stimulation is attenuated following habituation to a repeated mild stressor (restraint stress). When forskolin-induced synaptic potentiation was further investigated in naïve mice, we found that inhibitors for hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (a target for cAMP) abolished the forskolin-induced synaptic potentiation. In contrast, inhibiting protein kinase A (PKA), exchange protein directly activated by cAMP (EPAC) or extracellular signal-regulated kinase (ERK) did not prevent the forskolin-induced potentiation. This result highlights a possible mechanism for stress habituation (the attenuation of cAMP-mediated synaptic transmission) and suggests a role for HCN channels in PVN-CRH synaptic transmission.

2-B -44 Activity-dependent release of netrin-1 recruits GluA1 AMPA receptors to unsilence excitatory synapses in the adult hippocampus.

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Netrin-1 is a secreted protein that directs axon guidance during development, but little is known about its role in adulthood. Netrin-1 is enriched at synapses and expressed by excitatory neurons in the adult mouse hippocampus, suggesting roles in synaptic plasticity and in learning and memory. Genetic deletion of netrin-1 from forebrain excitatory neurons results in LTP attenuation and spatial memory deficits. We show that depolarization of hippocampal neurons increases extracellular netrin-1, suggesting activity-dependent netrin-1 secretion. Transient application of netrin-1 to hippocampal slices is sufficient to induce a long-lasting potentiation of Schaffer collateral-evoked postsynaptic currents in CA1 pyramidal neurons. We provide evidence that netrin-1 triggers GluA1 AMPA receptor (AMPARs) recruitment to the plasma membrane, including netrin-1-induced insertion of super-ecliptic pHluorin-tagged GluA1 at synaptic sites. Consistent with GluA1 synaptic recruitment, netrin-1 increases phosphorylation of CaMKII and of serine residues on GluA1 that regulate receptor trafficking. We show that netrin-1 increases the volume of thin-type dendritic spines and the frequency of miniature AMPAR-mediated excitatory postsynaptic currents with no detected change in presynaptic function. Using a minimal-intensity stimulation protocol, we demonstrate that netrin-1 unsilences glutamatergic synapses in adult hippocampal slices. These findings identify a novel role for activity-dependent release of netrin-1 in recruiting GluA1 AMPARs to mediate synaptic unsilencing in the adult brain.

2-B -45 Regulation of TRPM2 channels by Fyn kinase: Implications for Alzheimer's disease

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TRPM2 is a calcium-permeable nonselective cation channel gated by oxidative stress and implicated in neurodegenerative diseases. Our recent work has shown that TRPM2 function is facilitated in response to amyloid-beta, moreover that genetic deletion of TRPM2 reduces pathological markers and cognitive decline in a Alzheimer's mouse model. Although, TRPM2 channels are shown to be active and contribute to AD pathology, the mechanism promoting TRPM2 activation are not known. In light of past work suggesting that TRM2 function is regulated by tyrosine phosphorylation, herein we test whether Fyn kinase, known to be hyper-activated in AD, regulates TRPM2 function. To begin with, we investigated

the potential role of Fyn kinase as a regulator of TRPM2 channel. Intracellular application of Fyn (1U/mL) potentiated TRPM2 currents in HEK293 cells expressing TRPM2 and in primary hippocampal neurons- an effect that was blocked by the Src family kinase inhibitor PP2 and more specifically by a Fyn inhibitory peptide. This inhibition was not reversed with intracellular application of high concentrations of ADPR (10 mM), suggesting that phosphorylation does not alter agonist binding. Co-immunoprecipitation experiments in TRPM2-HEK cells confirmed a physical interaction of Fyn with TRPM2. Additionally, the amount of tyrosine phosphorylation of TRPM2 was related to the activation state of Fyn kinase. Future studies will determine whether recruitment of Fyn is a key determinant of increased TRPM2 function by amyloid-beta.

2-B -46 Investigating hyperexcitability of DRG neurons as a result of alterations in ion homeostasis in EAE.

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Multiple Sclerosis (MS) is an autoimmune inflammatory disorder of the nervous system. Neuropathic pain is one of the most common symptoms of MS. Experimental autoimmune encephalomyelitis (EAE) is commonly used to study MS pathophysiology. This study aims to elucidate the role of ion channels in mediating pain hypersensitivity in the dorsal root ganglia (DRG). Lumbar DRGs extracted from EAE mice show a transient activation of the complement system along with infiltration of Iba1+ macrophages and CD4+ T-cells at onset. This is accompanied by a transient upregulation of GFAP and Kir4.1 in satellite glial cells (SGCs). PCR analysis of voltage-gated Na+ channels (Nav1.3, Nav1.7, Nav1.8, Nav1.9) and voltage-gated Ca2+ channels (Cav2.2, Cav2.3, Cav3.2) reveals a significant downregulation of Nav1.9 and Cav3.2 transcripts at onset and chronic time-points. Cav2.2 mRNA levels are also decreased at onset, only to recover by chronic disease. Furthermore, mRNA levels of Na+-Ca2+ exchanger, NCX1, remain relatively constant but a significant decrease in NCX1 protein levels in SGCs post EAE onset is seen. NCX2 mRNA and protein levels are only detectable at EAE onset. Na+/K+ ATPase protein levels are significantly elevated only at chronic disease. Electrophysiology of dissociated DRG neurons reveals that myelinated (medium and large, >28 m) neurons were more hyperexcitable at onset and chronic time-points as compared to CFA (see abstract Noh et al., 2017). Hyperexcitability of myelinated neurons as a result of impaired ion homeostasis may contribute to mechanical hypersensitivity seen EAE.

2-B -47 The transcriptional regulation of Neuroligin-1 by clock proteins CLOCK and BMAL1

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NEUROLIGIN-1 (NLGN1) is a post-synaptic adhesion molecule involved in the regulation of sleep and in psychiatric disorders. It is localized to glutamatergic synapses and participates in the regulation of glutamate receptors. Work from our lab suggests that the transcription of the Nlgn1 gene could be regulated by the transcription factors CLOCK and BMAL1 because we have observed that these factors bind to a sequence of the Nlgn1 gene promoter in vivo. However, if CLOCK/BMAL1 can directly activate Nlgn1 transcription is not yet known. Our project thus aims to verify if CLOCK/BMAL1 can activate transcription via the Nlgn1 promoter and to identify the sequence mediating transcriptional activation. To do this, luciferase assays have been performed in Cos-7 cells to assess luciferase expression under the control of a portion of the Nlgn1 promoter. In parallel, mutations of putative CLOCK/BMAL1 binding

sites have been introduced to identify precise nucleotides involved, and the modulatory role of the kinase GSK3beta, which regulates the CLOCK/BMAL1 complex, has been studied. Our preliminary results show a transcriptional activation via the Nlgn1 promoter by CLOCK/BMAL1, an inhibition of this activation by GSK3beta, and a reduced activation when specific nucleotides contained in a precise E-box are mutated. These findings will increase knowledge about the regulation of Nlgn1, and the fundamental relationship between mental health and sleep.

2-B -48 Development of a platform to investigate EAAT transport using the biosensor Cyto-iGluSnFR

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The neurotransmitter glutamate is critical for nearly every aspect of CNS function, and so disruption of glutamate homeostasis is a central feature of many neurological diseases. Therefore, making effective drugs to modulate glutamate transmission is a highly desirable goal. Attractive targets to achieve this goal are the Excitatory Amino Acid Transporters (EAATs). EAAT1 and EAAT2 are selectively expressed by glial cells, and they play a critical role in controlling glutamate bioavailability and recycling. Loss of EAAT function is a major contributor to excitotoxicity following epilepsy and stroke as well as neurodegenerative diseases such as glaucoma, ALS, Alzheimer's and Huntington's diseases. However, drugs with appropriate selectivity and pharmacokinetic properties that can directly modulate EAAT function do not currently exist, and there are no comprehensive in vivo platforms to directly investigate EAAT-dependent glutamate transport dynamics within cells. We are developing a platform for measuring glutamate transport in vitro and in vivo through Cyto-iGluSnFR, a new intracellular glutamate biosensor. We are optimising tools for high-throughput drug screening of EAAT-based glutamate transport in cell assays, and for high-resolution imaging of EAAT transport dynamics in mice. The Cyto-iGluSnFR platform is designed to further understanding of EAAT transport, accelerate the discovery of new drugs targeting EAATs and to facilitate their evaluation in pre-clinical models of disease.

2-B -49 Features of input hierarchy enacted by a novel, habenula-driven, protracted feed-forward inhibitory circuit in the raphe

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The habenulo-raphe pathway is believed to be involved in the orchestration of optimal behavioral responses to aversive, threatening or stressful environments. The mechanistic details of how the long-range input from the LHb to the DRN is organized, processed, and ultimately contribute to the core coding features of 5-HT neurons is largely unknown. Here, using a variety of optogenetic strategies in combination with whole-cell electrophysiology, we outlined a novel form of processing in this hub network. We first found that the LHb input to the DRN provides a direct monosynaptic glutamatergic input to 5-HT neurons that also triggers a classic, rapid, GABAAR-mediated feedforward inhibition. Intriguingly, however, train stimulation of the LHb input to the raphe rather triggered a fundamentally distinct form of feedforward inhibition. This hyperpolarizing response lasted for seconds, its induction was steeply dependent on the frequency of LHb inputs and was mediated by 5-HT released from local 5-HT neurons organized in an unsuspected recurrent network architecture. Thus, this functional organization in effect allows the implementation of a dynamically regulated hierarchical access to the remarkably expansive innervation provided by the 5-HT system. More broadly, it provides an effective

and perhaps generalizable means for an incoming neural pathway to outcompete, over long timescales, parallel inputs to a hub-like network.

2-B -50 A spike timing-dependent plasticity rule for single, distributed, and clustered dendritic spines
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Dendritic spines can undergo structural remodeling, and are the preferential site for the induction of long-term potentiation (LTP) and long-term depression (LTD). In a variant of LTP and LTD, known as spike-timing dependent plasticity (STDP), the sign and magnitude of the change in synaptic strength depends on the timing between spikes of two connected neurons. Here we developed a spine STDP protocol, in which two-photon glutamate uncaging over single or multiple spines, which mimics pre-synaptic release of glutamate (pre), was paired with postsynaptic spikes (post) in layer 5 pyramidal neurons. We found that: 1) pre-post pairs at timings that trigger LTP (STDP-LTP) produce shrinkage of the activated spine neck and a concomitant increase in its synaptic strength, and 2) that post-pre pairs that trigger LTD (STDP-LTD) decrease synaptic strength without affecting the activated spine shape. Furthermore, we tested weather this rule is affected by the activation of neighboring or distant spines. Our results show that the induction of STDP-LTP in clustered spines (< 30 µm apart) enhances LTP and the shrinkage of the neck. Finally, the induction of STDP-LTD in clustered spines (< 30 µm apart) fails to induce LTD and spine morphological changes. Moreover, LTD can be recovered when the STDP-LTD protocol is induced in spines separated by more than 30 µm. These results indicate that spines are the minimal functional unit of STDP, and that Hebbian STDP in single spines is not only dependent on spike timing, but also on the synaptic cooperativity of inputs directed to clustered spines.

2-B -51 Stable Purkinje cell axonal torpedoes in developing and young adult cerebellum
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Focal swellings in the axons of Purkinje cells, or torpedoes, have been observed in multiple human neurodegenerative diseases, as well as in animal models of ataxias and other neurodegenerative diseases. Similar developmental torpedoes have been observed in the juvenile rodent brain. Although Purkinje cell axonal torpedoes are hypothesized to contribute to disease pathology, our understanding of their impact on cerebellar and cellular function remains poor. To elucidate the role of Purkinje cell axonal torpedoes in developing and young adult cerebellum, we used transgenic L7-tau-eGFP mice that brightly label Purkinje cell axons. We observed developmental torpedoes after the first week of postnatal development whose density peaked at postnatal day (P)11 (where torpedoes were observed on 39.7 ± 2.5% of Purkinje cell axons, n = 674). Since previous studies have studied torpedoes using fixed tissue, the temporal dynamics of Purkinje cell axonal torpedoes has been unknown. Using time-lapse two-photon imaging in acute sagittal slices of cerebellar vermis that preserves axons in the slice, we found that Purkinje cell torpedoes were stable, moving on average only 1.57 ± 0.41 um along the axon over a 2-hour period of imaging (n = 20). Using targeted recordings from visually-identified Purkinje cells with or without torpedoes, we observed no differences in the firing rates or regularity of Purkinje cells. Taken together, our results suggest that torpedoes observed in developing and young adult cerebellum are stable over several hours and do not negatively impact cellular function.

2-B -52 Retinal astrocytes protect neurons against metabolic stress by inducing the PI3K pathway
Samih Alqawlaq[1], Izhar Livne-Bar[1], Darren Chan[1], Jeremy Sivak [1]

[1]*University of Toronto*

Maintenance of retinal function heavily relies on the support of astrocytes, which carry out key homeostatic roles to protect neurons from oxidative and metabolic stresses. We have demonstrated that astrocytes protect neurons from metabolic stress. The purpose of the current research is to identify mechanisms of astrocyte-secreted factors involved in regulating metabolic stress in retinal neurons. For these experiments, astrocyte conditioned media (ACM) was collected from our established primary culture model. ACM efficiently rescued glutamate-induced cell death in neuronal Ht22 cells, and in primary cortical neurons. Using this model as a platform, a small molecule screen was carried out to identify pathways that mediate the neuroprotection. The screen was carried out on a robotics platform, with validation in primary cortical neurons. The pharmacological screen prominently identified several inhibitors targeting the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathway. In validation studies, the PI3K inhibitor ZSTK474, and AKT inhibitor GSK690693 each eliminated 90% of ACM-mediated activity in both Ht22 cells and primary neurons. Western blotting showed that ACM treatment was sufficient to induce AKT phosphorylation by 30 minutes. These data demonstrate that the ACM neuroprotection is mediated through the PI3K pathway. As several potential corresponding PI3K inducers were identified in ACM, these findings will enable additional exploration of candidate targets to promote astrocyte secreted neuroprotective signals.

2-B -53 An α2,3 GABAA receptor synaptic switch associated with the KCC2 deficit in neuropathic pain: a therapeutic opportunity

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Loss of spinal inhibition has long been hypothesized to underlie pain hypersensitivity after peripheral nerve injury (PNI). But how GABAA and glycine receptor-mediated inhibition is modified has remained elusive. Here, we show a reduction in number of inhibitory synapses and of the K+-Cl- transporters KCC2 in the spinal dorsal horn after PNI. In contrast, this is accompanied with by an increase in GABAAR (but not GlyR) synaptic expression and a selective switch towards α2,3 GABAAR subunits. Consistently, GABAAR mIPSC decay kinetic was prolonged, enhancing Cl- load. BDNF administration replicated the synaptic GABAAR plasticity and blocking TrkB reversed the PNI-induced changes identifying BDNF-TrkB signaling as both necessary and sufficient to explain both synaptic GABAAR and KCC2 plasticity. Yet, KCC2 hypofunction likely mitigates the efficacy of benzodiazepine-induced analgesia. Rescuing Cl- transport with the KCC2-enhancer CLP257 potentiated analgesia by the α2,3- GABAAR preferring L838,417 benzodiazepine. These findings point to a double prong strategy for analgesia: targeting the proper GABAAR subtypes while restoring Cl- homeostasis.

2-B -54 Dopaminergic Modulation of Persistent Activity in the Anterior Cingulate Cortex

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The anterior cingulate cortex (ACC) in the medial prefrontal cortex (mPFC) has long been associated with the affective components of pain perception. In models of chronic pain, pyramidal neurons in layer 2/3 of the ACC display hyperexcitable characteristics. Hyperpolarization-activated HCN channels, highly expressed in the mPFC, have been reported to modulate neuronal excitability. The inward currents of these cAMP-gated cation channels (Ih) control the input resistance of cells and therefore play a major role in the function of normal and pathological cortical circuits. Previous studies have shown that D1

dopamine GPCRs (D1R), localized close to HCN channels, are responsible for up regulating cAMP. Using persistent firing as a model for cell excitability, our whole cell patch clamp results indicate that D1R activation is inhibitory in layer 2/3 pyramidal cells in the ACC, hinting at a dopaminergic control on prefrontal activity. In further studies we will investigate the nature of dopamine signaling mechanisms in the ACC, and the impact on cognitive functions in chronic pain conditions. Using an established mouse model for chronic neuropathic pain (SNI surgery), we will measure the effects of dopamine and dopamine receptor subtype-selective agonists on both cell excitability and nocifensive behaviors in vitro and in vivo.

2-B -55 Presynaptic determinants of the heterogeneity in synaptic function at a central synapse

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The heterogeneity of release probability (Pr) and short-term plasticity (STP) among synapses on the same population of neurons is a fundamental feature of the central nervous system, and thought to be important for underlying different dynamic range of information coding. However, the origin of synaptic heterogeneity remains unknown. We addressed this issue by taking advantage of the large size of the mouse calyx of Held synapse, where the morphological variability strongly correlates with, and predicts the differences in Pr, polarity of STP and fidelity of spiking (Grande and Wang, 2011). We have examined calcium dynamics in distinct compartments of different types of calyces. We found calcium transients being largest in the smallest compartments (swellings). Patch-clamp recordings showed higher calcium channel density in complex than simple calyces. Presynaptic injections of slow calcium buffer EGTA attenuated Pr and readily releasable pool more in complex calyces. Numerical simulation reveals larger coupling distance between calcium channels and synaptic vesicles in complex calyces. An elevated level of steady-state transmission in complex terminals supported by a larger calcium accumulation in swellings underlies the higher fidelity and lower EGTA sensitivity of postsynaptic spiking. Our data implicate differences in the density of calcium channels and their spatial coupling distance to synaptic vesicles as key elements underpinning the heterogeneity of presynaptic calcium transients and quantal parameters, ultimately leading to functional diversity of central synapses.

2-B -56 Mu opioid receptor function and localization in the anterior cingulate cortex

Maria Zamfir[1], Kevin Lancon[1], Samantha Locke[1], Aliza Ehrlich[1], Brigitte Kieffer[1], Alfredo Ribeiro-da-Silva [1], Philippe Séguéla[1]
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Morphine and its derivatives have long been used as analgesics. Their effects are mainly due to the activation of mu opioid Gi protein-coupled receptor (MOR) located in the pain processing pathway. Interestingly, MOR is expressed in the anterior cingulate cortex (ACC), a subdivision of the prefrontal cortex involved in higher order pain processing, such as the emotional and affective aspect of pain experience. Recent studies in rodents suggest that pain relief is dependent on endogenous opioids acting on their receptors in the ACC. Our investigation aims to determine the function and localization of MOR in the ACC. We perform whole-cell patch clamp recordings of layer 2/3 pyramidal cells in the ACC using acute sections from wild type C57Bl/6 mice. We bath apply DAMGO, a selective mu opioid receptor agonist, to observe the effect of MOR activation on cellular excitability. We found that roughly 60% of layer 2/3 pyramidal cells in the ACC are sensitive to DAMGO and they respond with a reversible decrease in cellular excitability. Furthermore, we found that activation of MOR can inhibit pharmacologically induced persistent firing in these cells. In brief, we demonstrate that activation of MOR results in changes in information processing of layer 2/3 pyramidal cells in the ACC. Our future

aims are to determine whether MORs are located pre- or post-synaptically in the ACC, and investigate changes in MOR expression and function under neuropathic pain conditions.

2-B -56 Mu opioid receptor function and localization in the anterior cingulate cortex

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2-B -57 LOSS OF THE MOLECULAR BRAKE, STEP61, CONNECTS BDNF-MEDIATED DISINHIBITION TO NMDAR POTENTIATION DURING PATHOLOGICAL PAIN PROCESSING WITHIN THE DORSAL HORN.

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The spinal dorsal horn is an essential network for both physiological and pathological pain processing. We have recently shown that in nerve-injured rats, BDNF-mediated disinhibition gates the potentiation of GluN2B-containing NMDA receptors through Fyn kinase activation at lamina I dorsal horn synapses (Hildebrand et al, Cell Reports, 2016). We aim to explore whether loss of an associated phosphatase, STEP61 (Xu et al, J Neurochem, 2015), mediates this pathological coupling in lamina I neurons in rodents, including following chronic inflammation. We paired patch-clamp electrophysiological recordings with pharmacology, behavior, and biochemical approaches to explore mechanisms of lamina I NMDAR dysregulation. An ex vivo BDNF model of spinal pathology and an in vivo injection of Freund's adjuvant into the hindpaw was used to model pathological pain. In all models, we observed a decrease in STEP61 and an increase in pGluN2B and pFyn at lamina I synapses. Downregulation of STEP61 was both necessary and sufficient to prime subsequent phosphorylation and potentiation of synaptic NMDARs by BDNF. Importantly, we also showed that inflammatory pain hypersensitivity was reversed by attenuating disinhibition using IP injected acetazolamide, and paired this with biochemical analysis to investigate lamina I synaptic signalling. Our results suggest that STEP61 is the molecular brake that is lost to drive potentiation of NMDAR responses following BDNF-mediated disinhibition at lamina I synapses. Thus, STEP61 modulation may be a useful pharmaceutical target for treating pathological pain.

2-B -58 Structural Basis of AMPA Receptor Kinetic Regulation by TARPs and CNIHs

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Auxiliary proteins co-assemble with AMPA-type ionotropic glutamate receptors (AMPARs) to regulate their trafficking and functional properties at excitatory synapses. For auxiliary proteins such as transmembrane AMPA receptor auxiliary proteins (TARPs) and protein cornichon homologs (CNIHs), little is known about the molecular and structural mechanisms underlying these protein-protein interactions. Here, we used a combination of patch-clamp electrophysiology and site-directed mutagenesis to dissect the molecular determinants of TARP- and CNIH-dependent modulation of AMPAR gating properties. Single point mutations of charged residues in the lower lobe of the ligand-binding domain (LBD) of GluA2 AMPARs highly attenuated the ability of auxiliary proteins to slow decay kinetics. These findings demonstrate the electrostatic nature of the functional interaction between AMPARs and auxiliary proteins, and add to the growing body of evidence linking the lower LBD lobe as a hotspot for auxiliary protein modulation of AMPARs.

2-B -59 The dependence of IKCa and Kv7 channels on calcium sensors in activating the slow afterhyperpolarization in CA1 pyramidal neurons

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A long duration slow AHP (sAHP) in rat CA1 hippocampal pyramidal cells is calcium-dependent and involves activation of the intermediate conductance calcium-gated potassium channel KCa3.1 (IKCa) and KCNQ (Kv7) channels. Both IKCa and Kv7 channels bind calmodulin (CaM), but recent work proposed that the protein hippocalcin may act as the calcium sensor for potassium channels underlying the sAHP. We tested the relationship between IKCa and Kv7 to CaM and hipppocalcin, and measured the calcium sensitivity of the IKCa- or Kv7-mediated IsAHP. In whole-cell recordings the amplitude of the IKCa-mediated IsAHP increased over 10 min of internal infusion of 0 µM calcium, but decreased upon infusing 1 µM calcium. In contrast, the Kv7-mediated IsAHP responded in an opposite manner by decreasing with infusion of 0 µM calcium. IKCa and CaM exhibited coimmunoprecipitation (co-IP) that was lost for calcium levels of 1 µM or above. A co-IP between IKCa and hippocalcin was also found but only for calcium levels above 1 µM, suggesting a CaM-hippocalcin exchange as calcium increased. In contrast, Kv7 channels were constitutively bound to CaM at all calcium levels, with no association with hippocalcin. The results reveal that both IKCa and Kv7 channels are associated with CaM at low calcium levels, with a dynamic exchange of CaM and hippocalcin with IKCa that is consistent with a reduction in IsAHP amplitude as an increase in calcium removes CaM as a calcium sensor. Supported by CIHR OOGP (RWT, GWZ), CSM and HBI studentships (JM), and a AIHS PDF (GS).

2-B -60 Metaplasticity at CA1 synapses by homeostatic control of presynaptic release dynamics

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Hebbian and homeostatic forms of synaptic plasticity operate on different time scales to regulate synaptic strength. The degree of mechanistic overlap between these plasticity processes, and their mutual influence, are still incompletely understood. Here, we found that the homeostatic synaptic strengthening that develops in response to prolonged network inactivity was accompanied by a compromised ability of CA1 synapses to exhibit LTP. This effect could not be accounted for by an obvious deficit in the postsynaptic capacity for LTP expression, since neither the fraction of silent synapses nor the ability to induce LTP by two-photon glutamate uncaging were reduced by the

homeostatic process. Rather, optical quantal analysis revealed that homeostatically strengthened synapses displayed a markedly reduced capacity to maintain glutamate release fidelity during repetitive stimulation, ultimately impeding the induction, and thus expression, of LTP. By regulating short-term dynamics of glutamate release, the homeostatic process influences key features of dynamical network function and exhibits features of metaplasticity.

2-B -61 The Translation Repression 4E-BP is Necessary for Cerebellar Long Term Depression

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Rapid motor learning involves plasticity at parallel fiber (PF)-Purkinje cell synapses in the cerebellar cortex. LTD at these excitatory synapses depends on large calcium transients, usually mediated by P/Q channels, that activate PKC and CaMKII; whereas, LTP at PF synapses involves protein phosphates 1, 2A and 2B. Disrupting PKC or CaMKII signaling in Purkinje cells abolishes LTD and prevents motor learning. Synaptic plasticity at PF synapses also depends on de novo mRNA translation, yet the link between synaptic plasticity at PF synapses and mRNA translation is poorly understood. It has been shown recently, however, that eliminating the translation repressor 4E-BP impairs motor learning; therefore, we asked whether removing 4E-BP also impairs PF synaptic plasticity. To test this, we recorded parallel fiber EPSCs in acute cerebellar slices of 1 month old 4E-BP knockout and wild-type mice, and induced LTD by pairing PF stimulation with Purkinje cell depolarization. In wild-type cerebellum, this stimulation produced a strong LTD at PF synapses. Surprisingly, however, in 4E-BP mice, we observed PF LTP instead of LTD, indicating that in the absence of 4E-BP, the plasticity of PF synapses is reversed. Importantly, we show that the LTP in 4E-BP cerebellum could revert to LTD when we inhibited protein phosphates 2A, but not by manipulating the activity of other kinases and phosphatases. Our results show that regulating mRNA translation of PP2A through a 4E-BP mechanism is crucial for cerebellar LTD and may have implications for rapid motor learning.

2-B -62 Cortical Astroglial Plasticity in Response to Stress and Antidepressant Treatment

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An emerging body of work has suggested a potential role for astroglial cells in both the etiology and treatment of depression. Using transgenic mice (AldH-L1) that express green fluorescent protein (GFP) in astroglial cells, we employed a chronic unpredictable stress (CUS) paradigm in conjunction with chronic administration of the selective serotonin reuptake inhibitor (SSRI), fluoxetine, as an antidepressant treatment (ADT). Changes in behaviour and in cortical astroglia were examined using a variety of techniques across all groups. As expected, CUS significantly increased anxiety and depressive-like behaviours, however ADT did not reverse the effects, and, in some cases exacerbated the effect of stress. Using immunohistochemistry, we found that the total number of astroglial cells (as marked by constitutive astroglial-specific GFP) in the cortex did not change in response to stress or treatment, but their expression of intermediate filament proteins did. Moreover, stress induced markers associated with astroglial stem cell potential, including Sox2 and Vimentin. Finally, gene expression changes were examined using translating ribosome affinity purification (TRAP) in conjunction with RNASeq and major pathway clusters were identified including changes in extracellular matrices, glutamatergic signalling, growth factors and drug addiction. Together, these data suggest tremendous plastic responsivity of astroglial cells in response to chronic stress. Future studies will examine the causal involvement of differentially expressed pathways in response to stress.

2-B -64 MOLAR TOOTH EXTRACTION IN ADULT C57BL/6 MALE MICE ALTERS THE EXPRESSION OF THE ASTROGLIAL ENZYME GLUTAMINE SYNTHETASE IN THE OROFACIAL SENSORIMOTOR CORTEX

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Background: Molar tooth extraction in rodents induces decreased representations of jaw and tongue muscles and decreased excitability of the orofacial sensorimotor cortex (oSMCx)(1), as well as increased number of GFAP (glial fibrillary acidic protein)-labelled astroglia (2). Glutamine synthetase (GS) is a specific astroglial enzyme that converts glutamate to glutamine, a precursor of glutamate and GABA at excitatory and inhibitory synapses, respectively. Inhibition of GS can reverse the decreased oSMCx excitability induced by acute dental stimulation (3). Consistent with other studies, these studies suggest that astroglia play a role in oSMCx neuroplasticity induced by oral tissue injury but the exact mechanisms are still unknown. The Aim of this pilot study was to test if the expressions of GS and GFAP in the oSMCx are altered following tooth extraction in mice. Methods: Mice received either extraction of the right maxillary molar teeth or sham operation (n=6/group). Post-mortem western blot analysis quantified GS and GFAP expression in the oSMCx. Results: Tooth extraction was associated with decreased expression of GS and with no change in GFAP expression in the oSMCx. Conclusion: Together with our previous studies, the present novel findings suggest that activation of astroglia and upregulation of GS (but not GFAP) may be involved in the mechanisms underlying oSMCx functional plasticity and associated altered orofacial sensorimotor functions induced by tooth extraction. [Avivi-Arber et al: (1) J Comp Neurol 2015; (2) Dysphagia 2016; (3) Exp Br Res 2015].

2-B -65 Neuronal swelling during spreading depression involves the new Cl- channel, Slc26a11

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Cortical spreading depression (CSD) is a transient wave of neuronal depolarization propagating across the neocortex followed by periods of electrical silence. CSD is implicated in neurological diseases such as stroke, traumatic brain injury, and migraine aura. During CSD, morphological changes of neurons include swelling of the soma and dendritic beading ("bead on a string" appearance). A previous study in the lab identified a chloride channel, SLC26A11, as an essential component mediating neuronal swelling during cytotoxic edema (Rungta et al (2015) Cell). We hypothesized that neuronal depolarization induced chloride entry through activating the SLC26A11 channel, creating an osmotic force which consequently drives water entry and finally leads to neuronal swelling. Given that CSD also involves neuronal depolarization and neuronal swelling, the aim of this study is to investigate the role of the SLC26A11 channel in neuronal swelling during CSD and its contribution to other features of CSD. Two photon optical imaging with simultaneous field potential recordings were adopted to measure neuronal swelling, eletrophysiological and other optical signatures of CSD in the primary somatosensory cortex in GFP transgenic mice. We found that neuronal swelling was significantly reduced by GlyH-101, an inhibitor of the SLC26A11 chloride channel. However, electrophysiological and optical characteristics of CSD were mostly unaffected by GlyH-101. These observations shed light on the sequence of events during CSD and help dissect out individual components of these events.

2-B -66 The Role of Synapsin II in the Phencyclidine Pre-Clinical Rat Model of Schizophrenia

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Schizophrenia (SZ) is a mental disorder characterised by positive symptoms, negative symptoms, and cognitive dysfunction. Phencyclidine (PCP)--a N-methyl-D-aspartate (NMDA) receptor antagonist--induces symptoms indistinguishable from those of SZ. The study assessed short- and longer-term biochemical effects of NMDA receptor antagonism, which have implications for the pathophysiology of SZ. Sprague Dawley rats were implanted subcutaneously with osmotic mini-pumps containing saline or PCP (15mg/kg/day) for 14 days. The rats were then tested on behavioral paradigms, including locomotion (positive symptoms), social interaction (negative symptoms), and pre-pulse inhibition (PPI). A second cohort was treated with PCP twice a day for 7 days followed by 7 days of drug withdrawal. Brain regions of both cohorts were isolated for protein analysis post-treatment. Compared to saline-treated rats of the first cohort, PCP-induced rats demonstrated a hyper-locomotive state ($p<0.05$), reduced social interaction ($p<0.01$), and reduced PPI ($p<0.001$). While mPFC synapsin II levels of the first cohort were reduced in PCP-treated rats compared to the saline group ($p<0.001$), PFC synapsin II levels in the second cohort were increased ($p<0.05$). The behavioral outcomes produced validate the PCP model of SZ. The differences in synapsin II levels in the acute and non-acute testing regimens suggest underlying mechanistic differences between the immediate and longer-term consequences of NMDA receptor antagonism, offering novel insights into the pathophysiology of SZ. This work was funded by CIHR.

C - Disorders of the Nervous System

2-C -67 Modelling the Progression of Olfactory Deficits in Alzheimer's Disease using Caenorhabditis elegans

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Objective:Many cases of familial Alzheimer's disease (FAD) are linked to mutations of the presenilin (PS) genes. These genes are orthologous with sel-12 genes in Caenorhabditis elegans. Olfactory dysfunction is an early symptom of AD. We investigated the progression and underlying mechanisms of this dementia-linked deficit to understand its relationship with PS1 mutations. Methods:Chemotaxis experiments were conducted on worms with a mutation in sel-12. We examined various stages of the worm's life cycle to determine when this deficit appeared, and tested adult worms at 10 hour intervals. This provided novel insights into the dynamics of PS1 mutations and its subsequent effect on cellular pathways involved in chemosensation. Since C.elegans are innately repulsed by the odorant octanol and attracted by the odorant diacetyl, we utilized these two odorants in chemotaxis assays to assess the olfactory function of sel-12 mutants. Results:Adult sel-12 mutants had a significantly decreased sensitivity to octanol and diacetyl compared to wild-type worms. Introducing human wild-type PS1 into the nervous system of C.elegans rescued olfactory defects, while a PS1 mutant from Alzheimer's patient did not.Moreover, C.elegans sel-12 mutants presented olfactory deficits from hatching, and this deficit increased as worms aged, similar to the neurodegenerative progression of AD. Conclusions:This study demonstrates that mutations in C.elegans orthologue of PS1 are associated with altered chemosensation, and that these deficits were rescued by wild-type human PS genes in the nervous system.

2-C -68 Aged MTHFR mice show increased vulnerability to neurodegeneration and motor impairments after ischemic damage to the sensorimotor cortex

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Elevated plasma levels of homocysteine are an independent risk factor for cardiovascular disease, such as stroke. Folates are B-vitamins that are involved in reducing levels of homocysteine. This is achieved through methylenetetrahydrofolate reductase (MTHFR), an enzyme that breaks down folate so that it can remethylate homocysteine to methionine. Approximately, 15-20% of the North American population have a polymorphism in Mthfr resulting in reduced enzyme activity, elevated homocysteine levels and an increased risk of stroke. The association between MTHFR and increased risk for stroke is not well understood. The aim of this study was to determine whether MTHFR deficient mice were more vulnerable to ischemic damage. Aged (~18-month-old) male MTHFR deficient (Mthfr+/-) and wild-type littermate mice were subject to ischemic damage using the photothrombosis model to the sensorimotor cortex. Post-operatively, motor function was assessed and brain tissue was assessed for damage. Mthfr+/- mice displayed greater motor impairment on the skilled reaching and walking tasks, despite similar infarct volumes. At the damage site of brain tissue, we observed increased apoptosis and antioxidant activity in Mthfr+/- mice. Also, Mthfr+/- mice showed decreased microglial activation when compared to wildtypes at the damage site. These findings suggest that an MTHFR deficiency increases vulnerability to neurodegeneration and negatively impact functional outcome after ischemic damage.

2-C -69 BDNF, Calcium and Homeostatic Plasticity in Cultured Cortical Pyramidal Neurons from the YAC128 Mouse Model of Huntington Disease

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Huntington disease (HD) is a neurodegenerative disorder caused by a polyglutamine expansion in the huntingtin protein, producing mutant huntingtin (mHtt). The beginning of HD is marked by dysfunction at the cortico-striatal synapse and death of striatal projection neurons (SPNs), following prodromal psychiatric symptoms. Many pre- and postsynaptic proteins interact with mHtt, and the function of at least some of these proteins is affected by the disease-causing mutation. We set out to examine deficits in homeostatic plasticity - changes to neuronal function which maintain homeostasis in neuronal networks - at excitatory synapses onto cortical pyramidal neurons in primary neuronal cultures from wild-type FVB/N and the YAC128 mouse model of HD. To do this we tested neurons' response to 48-hour silencing of action potentials with tetrodotoxin. This produced an increase in the frequency of miniature excitatory postsynaptic currents relative to treatment with vehicle control in neurons from wild-type, but not YAC128, mice, suggesting an impairment to homeostatic plasticity. We have since been investigating potential mechanisms by which this impairment might occur. Current candidates involve brain-derived neurotrophic factor (BDNF) signaling and calcium sequestration. We have been examining their effects on the distribution and function of excitatory synapses, and how this is impacted by HD. This will allow us to better understand the dysfunction occurring in cortical pyramidal neurons, and how this may contribute to early psychiatric symptoms of HD and later death of SPNs.

2-C -70 Zebrafish models to validate mutations in CAPN1 causing hereditary spastic paraplegia

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Hereditary spastic paraplegia (HSP) is a genetically and clinically heterogeneous disease characterized by spasticity and weakness of the lower limbs due to the degeneration of upper motor neurons. Our collaborators performed whole-exome sequencing to analyze three families with autosomal-recessive HSP and mutations in CAPN1 were identified in all affected individuals (spastic paraplegia 76 [SPG76], Gan-Or et al., AJHG 98:1038-46, 2016). CAPN1 encodes calpain 1, a protease that is widely present in the

CNS. We validated calpain 1 deficiency using zebrafish with antisense morpholino (Mo). Knockdown of calpain 1a, a CAPN1 paralog in Danio rerio, resulted in several developmental defects visible at 2 days post-fertilization (dpf). The capn1a Mo was injected in the Islet1::GFP transgenic fish expressing GFP in the upper branchiomotor neurons. We observed a disorganization and migration defects of these motor neurons in comparison to those of the control. Additionally, reduced acetylated-tubulin staining could be observed at the level of the optic tectum and cerebellum and clusters of acetylated tubulin could be observed in some cells in the dorsal-most part of the brain. In order to further study calpain 1a deficiency in the zebrafish, we generated CRISPR/Cas9 knockout lines of both paralogs of CAPN1, calpain 1a and calpain 1b, and crossed these lines together to obtain a complete calpain 1 knockout. The identification of mutations in CAPN1 in HSP and the study of the resulting deficiency in the zebrafish expand our understanding of the disease causes and potential mechanisms.

2-C -71 Absence of evidence supporting the contribution of rare genetic variants in STK32B, PPARGC1A, CTNNA3 as genetic risk factors for Essential Tremor in a cohort of Canadians of European decent.

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A two-stage genome-wide association study (GWAS) that included 2,807 cases and 6,441 controls of European descent recently reported associations between essential tremor (ET) and specific intronic variants within three genes: STK32B, PPARGC1A, CTNNA3. The present report examined rare variants across the coding regions of these genes to further assess their role as ET predisposing factors. We first looked at high-throughput sequencing data from 14 of our autosomal dominant multiplex ET families but no rare deleterious variant was found to segregate with the disease. We than used a targeted massive parallel sequencing approach to examine the protein-coding region of these genes in 265 ET cases and 283 control individuals. Overall 34 variants were identified but no difference emerged regarding the distributions of individual variant (or gene) between cases and controls. Thus no rare exonic variants further validated one of these genes as a risk factor for ET. The recent GWAS offers promising avenues but the genetic heterogeneity of ET is nonetheless challenging for the validation of risk factors, ultimately larger cohorts of cases should help to overcome this task.

2-C -72 Protracted post-traumatic neuronal death in the developing hippocampus

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In the present study we evaluated the death of neurons in a chronically epileptic in vitro preparation in which multiphoton microscopy could be performed over a period of several days. Organotypic hippocampal slice cultures were made from wild-type C57BL/6J mice, and imaged with transgenic fluorophores as well as the Na+ dye SBFI. Immediately post-trauma, neurons had significantly higher [Na+]i than has been reported in undamaged neurons. After a brief recovery period, [Na+]i again rose to high levels and remained elevated for days. Elevated [Na+]i followed decreased synthesis of virus-induced fluorescent proteins such as TurboRFP, preceded morphological changes such as cell shrinkage and retraction of processes, and coincided with increases in membrane permeability (allowing for the passive influx of dyes and stains). The high [Na+]i was mitigated by the activity of Na+/K+ ATPases,

cation/Cl- cotransporters, and Na+/Ca2+ exchangers in order to support high rates of transmembrane Na+ flux during epileptogenesis. Inhibition of COX-2 and the protein Bax significantly lowered [Na+]i, suggesting that an apoptotic pathway leading to the insertion of permeability pores in the cytoplasmic membrane may be responsible for the rise in [Na+]i and related changes. Overall, a stereotypical sequence of events preceded neuronal death by at least several days, beginning with quenched emission of fluorescent proteins, dendritic retraction, elevation in [Na+]i , and terminal cell shrinkage. ATPase activity and secondary ion transport remained robust throughout this process.

2-C -73 DNA methylation within the TH gene is associated with cocaine dependence in humans.
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Background: Cocaine dependence is a chronic relapsing disorder with widespread biological consequences, including epigenetic alterations, in numerous brain areas. Methods: We used Reduced Representation Bisulfite Sequencing (RRBS) to identify genome wide differentially methylated regions (DMRs), in 25 dependent cocaine users and 25 controls, in the nucleus accumbens (NAc) and caudate nucleus (CD). We replicated a DMR within the tyrosine hydroxylase (TH) gene using bisulfite sequencing, and used fluorescence activated cell sorting (FACS) to identify cell-type specificity. In addition, we used an animal model of chronic cocaine seeking, transcriptional assays and in vitro experiments to elucidate the relationship between methylation, expression and transcription factor binding on this system. Results: We found numerous DMRs in both brain regions, including within exon 8/9 of TH that are more methylated in the cocaine group. Methylation negatively correlates with TH expression in the CD of the cocaine group. We replicated this effect in the NAc of an independent cohort (N=18 per group), and of chronically self-administering mice (N=8-10 per group). This hypermethylation appears to be neuron-specific and impedes enhancer activity at this locus. Conclusions: Hypermethylation of TH is associated with chronic drug seeking behavior and may have regulatory potential. Further research will uncover the functional relationship between epigenetic dysregulation of TH and the time course and trajectory of chronic cocaine dependence. Funded by NIDA (DA033684).

2-C -74 Parkin KO dopamine neurons of the substantia nigra, show altered survival, mitochondrial oxidative phosphorylation and axonal growth.
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Mutations in gene products such as Parkin, Pink1, DJ-1, LRRK2 and α-synuclein have been linked to familial forms of Parkinson's disease (PD). Although the consequences of these mutations, such as alterations in mitochondrial function and pathological protein aggregation, are starting to be better understood, little is known about the reasons why alterations in such ubiquitous cellular mechanisms lead to selective loss of restricted subsets of neurons, including substantia nigra (SNc) dopamine (DA) neurons. Recent work showed that one of the reasons underlying the high vulnerability of SNc DA neurons is their particularly high basal rate of mitochondrial oxidative phosphorylation (OXPHOS), which appears to be a consequence of their highly complex axonal arborization. Here we examined whether axonal growth and basal mitochondrial function are altered in postnatal SNc DA neurons cultured from Parkin KO mice. We provide evidence for increased basal OXPHOS and reduced survival of neurons with complex axonal arbors in Parkin KO culture. The remaining neurons, having a smaller axonal arborization, show reduced vulnerability to MPP+, associated with reduced expression of the DA

transporter. Finally, we provide evidence for an implication of glial cells in this reduced resilience. Strikingly, culture of Parkin KO neurons with WT astrocytes prevented neuronal loss. Our data provides new insights into the complex relationship between mitochondrial function, axonal growth, glial cell function and genetic risk factors linked to PD. Work funded by the Brain Canada and Krembil foundations

2-C -75 Investigating the protective effects of mitochondrially targeted telomerase reverse transcriptase on neuronal metabolism under oxidative stress and sensitivity to amyloid-beta.

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Telomerase consists of two main components that function as dimers; the telomerase RNA component (TERC) and the telomerase reverse transcriptase (TERT). TERT catalytically adds TTAGGG repeats to the lagging strand of chromosomes thereby preventing telomere shortening during DNA replication in mitotic cells. However, there is increasing evidence for non-telomeric functions of TERT in post-mitotic cells. Under oxidative stress conditions, TERT can translocate from the nucleus to the mitochondria and promote a decrease in mitochondrial reactive oxygen species (ROS) production while increasing mitochondrial membrane potential. Mitochondrial dysfunction is a prominent feature of many neurodegenerative diseases including AD. A major pathological feature of AD is the progressive accumulation of amyloid-beta (Aβ) peptide within the cortex and hippocampus, which can directly interfere with mitochondrial respiration and promote mitochondrial dysfunction, ROS production, and cell death. Hence, we hypothesized that TERT may protect neurons from mitochondrial dysfunction and Aβ toxicity via metabolic reprogramming. We transfected the murine hippocampal neuronal cell line HT22 cell cultures with a TERT overexpressing plasmid. TERT overexpression in HT22 cells resulted in altered glycolytic enzyme activity, mitochondrial membrane potential and ROS production. We are currently determining if TERT localizes to mitochondria and confers neuroprotection against Aβ toxicity via metabolic reprogramming. The results from this study may lead to a novel potential therapy for the treatment of AD.

2-C -76 Patient-like loss-of-function of Glycine Decarboxylase recapitulates glycine encephalopathy in zebrafish

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Glycine encephalopathy (GE) is an inherited metabolic disorder due to a defect in the glycine cleavage system, such as the glycine decarboxylase (GLDC). GE patients, in which GLDC sequence is frame-shifted, have elevated glycine levels in body fluids and demonstrate developmental delay, lethargy and hypotonia. However, the treatments currently available for the patients have limited efficacy since the cause of the defect is largely unknown. Generating a zebrafish model of GE would allow to recapitulate the disease in a simple and easy-to-use organism and ultimately test various drugs to rescue the phenotype. We generated a gldc knockout mutant in zebrafish using CRISPR-based technology and have shown by LC-MS that gldc-/- embryos exhibit higher levels of glycine as observed in GE patients. Importantly, the gldc-/- mutants show a clear phenotype of motility impairment, which makes them easily discernable from their siblings. The motor defects are composed of decreased swimming, problems with stabilizing against a water current, and increased floating on the water surface. Interestingly, the buoy mutants also die prematurely at 7 days. Thus, the phenotype of those buoy mutants recapitulates the motor defects observed in GE patients. Overall, this zebrafish knockout line recapitulates GE condition molecularly and phenotypically. We now aim at studying the underlying

molecular mechanisms of the disease using RNA sequencing. Moreover, we plan on screening for small molecules that would rescue the buoy phenotype and be the first potential treatment for GE.

2-C -77 Glial HO-1: A driver of Parkinson-like neurodegeneration in aging mice

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Idiopathic Parkinson disease (PD) is a movement disorder that afflicts 1-2% of the population over 65 years of age. Epigenetic effects mediating brain iron deposition, oxidative mitochondrial injury and macroautophagy in PD and related conditions remain enigmatic. Here, we show that selective overexpression of the stress protein, heme oxygenase-1 (HO-1) in astrocytes of GFAP.HMOX1 transgenic mice between 8.5 and 19 months of age results in a parkinsonian phenotype characterized by basal ganglia siderosis; oxidative stress; mitochondrial damage/mitophagy; nigrostriatal hypodopaminergia associated with locomotor incoordination and stereotypy; downregulation of TH, DAT, LMX1B, Nurr1 and Pitx3 mRNA and/or protein; and overproduction of alpha-synuclein mRNA and protein. We also identified altered levels of key brain microRNAs which may be responsible for the aberrant expression of Nurr1, Pitx3, DAT and alpha-synuclein in these mice. Many of the molecular changes we observed in the intact GFAP.HMOX1 brain were recapitulated in isolated neurons co-cultured with HMOX1-expressing astroglia indicating further that patterns of neuronal dysfunction commensurate with parkinsonism may be evoked by a primary insult to the astroglial compartment. Our findings raise the possibility that curtailment of glial HO-1 transduction may confer neuroprotection in idiopathic PD and other chronic CNS disorders.

2-C -78 Zebrafish hitch mutants, knockout for glycine receptor alpha 1 subunit, exhibits motor deficits associated with hyperekplexia.

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Hereditary hyperekplexia (HH), also called familial startle disease, is a very rare hereditary neurological disorder leading to a high risk of sudden infant death due to apnea attacks. The main causes of HH are mutations in genes of the inhibitory glycinergic network, in particular the alpha 1 and beta subunits of the glycine receptor (GLRA1 and GLRB). Our project aims at generating a predictive model of HH in zebrafish, characterizing the molecular and physiological abnormalities, and testing new therapeutic compounds targeting the glycinergic system to rescue the phenotype. Zebrafish has five glycine receptor alpha subunits encoded by distinct genes that we decided to knockout individually using CRISPR-based genome editing. For each of these five genes, we generated frame-shifting mutations disrupting the glycine binding domain of the protein and therefore abolishing the subunit function. Interestingly, loss of function of the alpha 1 subunit leads to a motor phenotype whereas none of the other subunit mutation is altering normal embryo development. Hitch mutants (glra1-/-) exhibit a motor phenotype characterized by an abnormal hitching of the tail at early stages. Later on, these embryos are not able to swim correctly and they die prematurely. As a result, the hitch mutant mimic HH condition and therefore represents a model of choice for further drug-screen assay. Indeed, using automated softwares that quantify the swimming behaviours of the embryos, we will screen for multiple compounds that could rescue the motor phenotype in a high-throughput fashion.

2-C -79 Repairing the Blood Brain Barrier Following Ischemic Stroke: Role of the Wnt/ β-catenin Pathway

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[1]CHUL

Canonical Wnt/β-catenin pathway plays key role in inducing blood brain barrier (BBB) formation and maturation during embryogenesis. Its role in the adult brain remains little explored. Recent findings are suggesting that the pathway might be deregulated upon stroke. BBB disruption constitutes a hallmark of ischemic stroke, and hampers tissue recovery by impairing local brain microenvironment. We aimed in this study to decipher Wnt/β-catenin pathway regulation and role at the BBB upon ischemic stroke using transient middle cerebral artery (MCA) occlusion in mice. Our data suggest that stroke stressors dynamically regulate the pathway at the BBB. In the acute phase the pathway is activated, while it is deactivated in the sub-acute phase. In order to elucidate the biological significance of this observation, the pathway was pharmacologically deactivated in the acute phase using Wnt inhibitor XAV939, and activated in the sub-acute phase using Wnt activator SB216763. Pathway early deactivation caused haemorrhagic transformation and increased brain oedema. On the other hand, pathway delayed activation reduced brain oedema. These findings indicate that Wnt/β-catenin pathway is required to maintain the structure and function of the BBB once stroke occurs. Thereby, pathway activation constitutes an elegant strategy via which it may be possible to achieve powerful therapeutic interventions that aim at preventing BBB breakdown in the acute phase and promoting BBB repair in the sub-acute phase. We hope that by promoting BBB structure and function tissue recovery could be stimulated.

2-C -80 Vascular endothelial growth factor isoform-B stimulates neurovascular repair by promoting pericytes function after ischemic stroke

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Brain microvasculature decisively supports neuronal survival and function. Hemodynamic disturbances associated to brain microvasculature destabilization upon stroke aggravate the neuronal damage. Strategies aiming to promote vascular density to compensate for these disturbances have been proposed to constitute a promising therapeutic approach. Most studies have investigated vascular endothelial growth factor isoform-A (VEGF-A), which is a potent angiogenic factor. However, enthusiasm was hampered by the elevated risk of exacerbating brain microvasculature destabilization. We aimed in this study to evaluate the therapeutic potential of VEGF isoform-B (VEGF-B), which act as a "survival" rather than "angiogenic" factor, using in vivo and in vitro approaches. Our data indicate that VEGF-B administration reduced neuronal damage and stimulated the formation of stable microvasculature within the injured region. Importantly, VEGF-B mediated these effects via its receptor VEGFR-1, which is predominately expressed in brain pericytes. VEGF-B promoted the survival of pericytes, but not brain endothelial cells, by inducing expression of the anti-apoptotic protein B-cell lymphoma 2 (Bcl2) and AMP-activated protein kinase α (AMPKα), a protein involved in energy homeostasis. Additionally, VEGF-B stimulated the pericytic release of factors stimulating a "reparative angiogenesis" which increased microvasculature stability. Our study suggests that VEGF-B may constitute an attractive safe strategy to promote vascular density and stability, and thereby stimulate ischemic brain tissue recovery.

2-C -81 Increased serotonin and dopamine pallidal innervations in MPTP-intoxicated monkeys

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This study was designed to characterize the neuroadaptive changes of serotonin (5-HT) and dopamine (DA) innervations that occur in the internal (GPi) and external (GPe) pallidal segments of cynomolgus monkeys rendered parkinsonian by MPTP injections. In control animals, the GPi is more densely innervated by 5-HT than the GPe (0.43 x 10^6 5-HT varicosities/mm^3 vs. 0.32). Intoxication with MPTP induces a two-fold increase in the density of 5-HT terminals in both pallidal segments. Ultrastructural features and synaptic incidence of 5-HT axon varicosities are similar between MPTP and control monkeys, in the GPi and the GPe. The primate pallidum is less densely innervated by DA than by 5-HT axons with 0.18 x 10^6 DA varicosities/mm^3 in the GPi and 0.14 in the GPe. A significant increase of the DA pallidal innervation is also noted following MPTP administration, and this augmentation is more pronounced in the GPi with 0.56 x 10^6 DA axon varicosities/mm^3. Our data reveal that both the DA and the 5-HT axons that innervate the primate pallidum are highly plastic and able to go through significant morphological reorganization following MPTP administration. In contrast to the massive degeneration of the nigrostriatal DA system that characterizes the PD state, the DA projections to the GPi appear to be preserved and even increased in PD monkeys. We hypothesize that, based on their remarkable resistance and flexibility in face of a major neurotoxic insult, the DA and 5-HT pallidal inputs play a significant role in the expression PD symptoms and L-Dopa-induced dyskinesia.

2-C -82 The clinically-available anti-depressant mirtazapine attenuates psychosis and dyskinesia in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned marmoset model of Parkinson's disease

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Psychosis and dyskinesia cause significant morbidity to as many as 50-95% of patients with advanced Parkinson's disease (PD). There is increasing evidence that serotonin 2A receptor (5-HT2AR) blockade may alleviate PD psychosis and dyskinesia. Mirtazapine is a clinically-available anti-depressant that acts through complex interactions with a breadth of targets, including 5-HT2AR. We hypothesised that mirtazapine is potentially efficacious to reduce PD psychosis and dyskinesia. Five marmosets were rendered parkinsonian by administration of MPTP. Stable and reproducible psychosis-like behaviours (PLBs) and dyskinesia were induced by administration of L-DOPA. Mirtazapine (vehicle, 0.1, 1 and 10 mg/kg) was then administered to the animals, in combination with L-DOPA, after which its effects on L-DOPA-induced dyskinesia (LID), PLBs and parkinsonism were determined. In combination with L-DOPA, mirtazapine (10 mg/kg) significantly reduced PLBs severity, by 50% ($P<0.05$), when compared to L-DOPA/vehicle. Moreover, mirtazapine (10 mg/kg) significantly reduced duration of on-time with disabling PLBs, when compared to L-DOPA/vehicle (by 64%, $P<0.01$). Mirtazapine (10 mg/kg) also reduced LID severity, by 29%, when compared to vehicle ($P<0.01$). Accordingly, mirtazapine (10 mg/kg) significantly reduced duration of on-time with disabling LID, by 71% ($P<0.01$), when compared to vehicle. Mirtazapine did not alter the anti-parkinsonian effect of L-DOPA. These results suggest that mirtazapine is a potential drug candidate to effectively reduce the severity of PD psychosis and dyskinesia.

2-C -83 Motor function in 3xTg-AD mice at 16 months of age

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Motor deficits are one of the most prevalent non-cognitive symptoms of Alzheimer?s disease (AD) as patients show impairments in speech, gait and fine motor skills. We investigated age-related changes in

motor behaviour in 16-month-old male and female triple-transgenic (3xTg-AD) mice and their B6129SF2 wildtype (WT) controls. The 3xTg-AD mice develop extracellular Aβ plaques and tau tangles in the hippocampus and motor cortex between 6 and 9 months of age. Stover and Brown (2015 Behav Brain Res, 281, 16-23) showed that 3xTg-AD mice performed better on motor tests than WT mice at 6 months of age. The aim of our experiment was to determine if this superior motor performance continued as the mice aged. On the Rotarod (6 trials/day for 5 days), the aged 3xTg-AD mice showed better motor coordination and learning performance than WT mice. Although females performed better than males, this sex difference was confounded by body weight as females weighed less than males. There were no significant genotype or sex differences on the wire hang or grid suspension tasks, nor in stride length or stride width in the analysis of gait. In comparison to the 6-month-old mice, Rotarod performance declined, stride length and width decreased, but there were no changes in grid suspension or wire hang performance. These results show the 3xTg-AD mice still display enhanced motor performance on the Rotarod, although the differences on other motor tests at 6 months of age were not present at 16 months of age. We continue to study the enhanced motor coordination and learning performance in 3xTg-AD mice.

2-C -84 Inactivation of the contralesional motor cortex after unilateral spinal cord injury impedes recovery of hindlimb motor function by preventing plasticity of the ipsilesional cortex.

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After unilateral spinal cord injury (SCI) at thoracic level in the rat, the lower limb on the side of the lesion is initially paralyzed but recovery typically occurs within 3 weeks. We recently found that at the time of recovery, plasticity of the ipsilesional motor cortex participates in the recovery of the affected hindlimb. What are the mechanisms triggering ipsilesional cortical plasticity after SCI? Activity in one cortex is known to promote changes in the contralateral homologous cortex. We herein tested whether residual activity in the contralesional motor cortex is necessary for inducing plasticity of the ipsilesional motor cortex that mediates recovery of the affected hindlimb. The contralesional motor cortex was inactivated for 3 weeks after SCI with muscimol (GABA-A agonist). Hindlimb motor function was assessed on a horizontal ladder and treadmill prior to and for 3 weeks after SCI. Rats with cortical saline infusion served as a SCI control group. In terminal experiments, intracortical microstimulation was used to derive hindlimb motor maps. Inactivation of the contralesional motor cortex after SCI significantly impeded recovery of the affected hindlimb in both behavioural tasks. Further, cortical inactivation prevented ipsilesional motor map plasticity from gaining control over the affected hindlimb. In conclusion, we propose that residual activity within the contralesional motor cortex during the initial recovery period after SCI is necessary for inducing plasticity of the ipsilesional motor cortex which, in turn, promotes recovery of hindlimb motor function.

2-C -85 Exercise alters response of reward anticipation in the ventral striatum of subjects with Parkinson's disease

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The benefits of exercise in PD have been linked to enhanced dopamine (DA) transmission in the striatum. It is hypothesized that exercise-induced changes in DA function may also alter reward signaling in the ventral striatum (VS). VS activity was examined with fMRI during a monetary incentive task.

Subjects selected 1 of 4 cards during a trial. Each block (20 trials), had a different probability of reward 0, 50, 75, 100%. Percent signal change of the BOLD signal was calculated prior to reward delivery (anticipatory phase). 2 different comparisons were completed: 1) Sedentary subjects (SED) vs. habitual exercisers (HAB) - 22 male subjects with PD, 15 SED subjects and 7 HAB exercisers. 2) Aerobic cycling (AER) vs. control/stretching (CON) - 21 sedentary subjects with PD were randomly allocated into AER (n=14) or CON (n=7) exercise interventions. Results: SED vs. HAB - HAB had higher BOLD signal at 75% probability compared to SED $t(20)= 2.27$, $p<0.05$). AER vs CON - Significant time x prob x group interaction. LSD post hoc showed a decrease in BOLD signal at 50% probability pre to post in CON and at 75% probability an increase in BOLD signal pre to post in only AER ($p<0.05$). Conclusions: At 75% probability HAB had a greater BOLD signal in the VS compared to SED. A similar response was seen after 3 months of aerobic exercise. The BOLD signal in the VS increased after 3 months of aerobic exercise, with no difference in the control group. This study suggests that aerobic exercise alters reward circuitry, potentially through changes in the mesolimbic DA system.

2-C -87 Shifting Cell Fate in the Midbrain: Implications for Development and Disease

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Lesch-Nyhan disease (LND) is an X-linked genetic disease characterized by neurological and behavioural disturbances, including dystonia and a compulsion to self-harm. LND is caused by mutations in the housekeeping gene HPRT1, which encodes the protein HPRT, an enzyme involved in the production of purines. Yet, despite the ubiquitous expression of HPRT, and the neurological symptoms that result from its absence, most neurons tolerate a loss of HPRT. However, multiple lines of evidence suggest that the deficiencies observed in patients with mutations in HPRT1 are due to deficits in a specific neuronal subtype, midbrain dopaminergic neurons. How mutations in a globally expressed metabolic gene can specifically impact a population of dopaminergic neurons has remained a mystery for over thirty years. To create a novel model of HPRT deficiency, we generated induced pluripotent stem cells (iPSCs) from patients with LND that had deficient HPRT activity and control patients. We differentiated these iPSCs into dopaminergic progenitor cells (DPCs), and assessed their gene expression profiles using RNAseq. To our surprise, DPCs from HPRT-deficient patients had a gene expression pattern that diverged from normal dopaminergic development and showed increased expression of genes related to the development of glutamatergic neurons. We then generated mature, electrically active neurons from these progenitor cells. In accordance with our previous results, mature neurons from HPRT-deficient patients had reduced expression of dopaminergic markers, and a concurrent increase in glutamatergic mar

2-C -88 Visual cortical network mapping following partial optic nerve injury

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Traumatic optic neuropathy damaging the optic nerve causes visual impairment and partial or complete loss of vision. Retinal ganglions cells degenerate, but there is still a residual vision mediated by surviving retinal cells and cortical plasticity. However, the cortical network reorganization over time after an optic nerve injury is still poorly understood. In the present study, we monitored the residual cortical function and its plasticity following monocular partial Optic Nerve Crush (ONC) across time. The neuronal calcium response to a monocular flash illumination was measured using in vivo wide-field calcium imaging on

awake mice (Thy1-GCaMP6s) at 1 hour and at 1, 3, 5, 7, 14, 23 and 31 days after the injury. The strength of long-range functional connections between areas of the visual cortex and high-order areas were quantified during visual recovery. Changes in intra- and inter-hemispheric cortical responses were observed post-ONC. The cortical response was weaker in the hemisphere receiving input from the injured eye compared to the pre-ONC values and weaker compared to the opposite hemisphere. An inter-hemispheric shift of the visual cortical response was also observed. In conclusion, our results show a reorganization of the connectivity between visual and associative cortical areas following traumatic optic nerve injury which is indicative of visual cortical plasticity. Specifically, our results suggest interhemispheric compensation in the primary visual cortex. These results open an interesting avenue to modulate visual recovery processes after visual deficit

2-C -89 Epigenetic impacts of stress priming of the neuroinflammatory response to sarin surrogate in mice: a model of Gulf War Illness

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Gulf War Illness (GWI) is an archetypal, medically unexplained, chronic condition characterised by persistent sickness behaviour, neuroimmune and neuroinflammatory components. An estimated 25-32% of the over 700,000 veterans of the First Gulf War fulfil the requirements of a GWI diagnosis. Patients with GWI continue to show debilitating symptoms 25 years after the conflict, a persistence consistent with the hypothesis that epigenetic modifications may contribute to disease pathology. It has been hypothesised that the high physical and psychological stress of combat may have primed the immune system to over-react to the low level of the irreversible AChE inhibitor, sarin, that many veterans were exposed to in the theatre of war. Recent research in a mouse model has shown that pre-treatment with the stress hormone corticosterone (CORT) causes an increase in expression of specific chemokines and cytokines in response to diiso-propyl fluorophosphat (DFP), a sarin surrogate. We are integrating transcriptome- and epigenome-wide approaches to further investigate combinations of exposure conditions associated with GWI in this mouse model. In the frontal cortex, RNA-seq results show that differentially expressed genes are enriched for immune related annotations, whereas H3K27ac ChIP-seq indicates differential binding to genes involved in regulation of neuron projection development. This project will show the epigenetic results of combined stress and exposure to an AChE inhibitor, potentially identifying pathways to understanding the etiology and treatment of GWI.

2-C -90 A role for brain pericytes in revascularization after stroke revealed by a novel reporter mouse.

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Brain pericytes are vascular mural cells that are a critical component of the neurovascular unit essential for blood brain barrier (BBB) integrity and developmental vessel maturation. However, their role in recovery following CNS trauma is unclear. Here we demonstrate that proliferating pericytes promote tissue revascularization following stroke. After focal photothrombosis-induced permanent ischemia, significant peri-lesional revascularization was observed over weeks using in vivo systemic fluorescein imaging and optical coherence tomography. To evaluate the role of pericytes in this process, a novel transgenic mouse was generated to obtain pericyte-specific tdTomato expression. Following pericyte death, a proliferative invasion of activated pericytes within the lesion core was observed. These

dysmorphic pericytes migrated to the edge of the ischemic area, lining the inner border of an astrogliosis barrier. Prior to blood flow reestablishment, pericytes showed perivascular morphology and associated with endothelial cells. We also observed overproduction of basal lamina components, all indicative of regional angiogenic activity, suggesting that pericytes form a progressive angiogenic front to drive revascularization. Furthermore, we show via dye extravasation experiments that proliferated pericytes within the revascularized cortical tissue promoted the maturation of a functional BBB. In conclusion, we provide a novel transgenic model for pericyte investigation and demonstrate a surprising role for pericytes in promoting revascularization following stroke.

2-C -91 Behavioural Investigations of Parkinson's Disease Associated Genes in Caenorhabditis elegans

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Parkinson's disease (PD) is a neurodegenerative disorder that affects more than 5 million people worldwide. Clinical symptoms include resting tremors, impaired dopamine signaling, and early signs of olfactory deficits. In familial PD, VPS35 and LRRK2 have been implicated as potential genetic correlates of PD. VPS35 mutations are linked to increased mitochondrial fission and impaired retromer function, whereas LRRK2 mutations are linked to mitochondrial dysfunction and increased autophagy-lysosomal function. Using C. elegans, we demonstrate behavioural abnormalities consistent with PD symptomology in worms carrying mutant copies of these genes. Worms with mutations in vps-35, the C. elegans orthologue of human VPS35 show chemosensory deficits, dopamine deficiency, and abnormal tap habituation. Furthermore, worms with mutations in lrk-1, the C. elegans orthologue of human LRRK2 show chemosensory deficits and abnormal tap habituation, but do not show dopamine deficient signaling. Future experiments will focus on rescuing these behavioural deficits with endogenous as well as wild-type and disease related mutations of human copies of the genes of interest in order to explore their underlying mechanisms.

2-C -92 Identification of a pharmacological suppressor of pathological axon degeneration that that acts by preserving mitochondria

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ABSTRACT Axon degeneration is an early event and pathological in neurodegenerative conditions and nerve injuries. To discover agents that suppress axon degeneration, we performed drug screens on primary rodent neurons, and identified the pan-kinase inhibitor Foretinib that rescued sympathetic, sensory, and motor neurons from trophic factor withdrawal-induced degeneration (also-known as die-back degeneration), and delayed chemotherapy-induced and Wallerian degeneration in culture and peripheral Wallerian degeneration in vivo. Foretinib was considerably more effective than other neuroprotective kinase inhibitors, and protected axons in die-back models by suppressing pro-degenerative kinases and the expression of pro-apoptotic genes such as BimEL known to compromise mitochondrial function. Specifically, Foretinib inhibited the activity of pro-degenerative JNK pathway kinases and unligand-bound TrkA, a new pro-degenerative kinase that we validated by pharmacological and chemical-genetic approaches. In Wallerian degeneration models where axons are severed from cell bodies, Foretinib appeared to protect axons by maintaining intracellular ATP levels. These findings identify a new pro-degenerative kinase and a potentially clinically-useful therapeutic that preserves mitochondria in the degenerative setting.

2-C -93 Proof of Concept: CRISPR-Cas9 Lipid Nanoparticles as an Efficient Delivery Tool for Cultured Cells and in Animal Models

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We describe the development of a lipid nanoparticle (LNP) delivery system for CRISPR components, manufactured using microfluidic technology. Lipid-based nanoparticles encapsulate and delivery different payloads, such as siRNA, mRNA and plasmid. In this proof of concept, we show that representative small RNAs, mRNAs and plasmids can be successfully delivered to primary neurons. LNPs manufactured to encapsulate various nucleic acids can do so with high efficiency, encapulating more than 95% of the payload, minimizing payload loss. Transfection efficiency of the LNPs is >95%, quantified using a flourescent dye. The biological endpoint assays used to determine the accessiblility of the payloads delivered varies for siRNA, mRNA and plasmid. Using doses of 1g per mL of media, we achieved >90% knockdown with siRNA delivery, >90% of the primary neurons are GFP+ with GFP mRNA delivery and >60% of the primary neurons are GFP+ with GFP plasmid delivery. The LNPs are well tolerated, such that 5x the required doses have no oberservable cytoxicity. We show that the LNPs can also be used to deliver payloads into various regions of the animal brain. The localized injections into the cortex and the striatum are well tolerated and have extensive distribution. These validation studies provide suitable insights in establishing strategies for efficiently delivering CRISPR components into primary cultures and into the animal. We have editing efficiencies associated with delivering gRNAs to Cas9-expressing cells, as well as simultaneously delivering Cas9 mRNA and gRNAs to cells.

2-C -94 Detecting intraneuronal Aβ in the human hippocampus by super-resolution microscopy

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Alzheimer's disease (AD) is the most prevalent form of dementia with patients exhibiting progressive cognitive decline and distinct pathological features within the brain, including toxic amyloid-β (Aβ) plaques. Although it is widely accepted that over-accumulation of Aβ is the precipitating factor of AD, precise molecular mechanisms mediating subsequent pathological events remain unclear. It has been shown by our lab and others' that Aβ first accumulates intraneuronally (iAβ) before the appearance of extracellular plaques both in humans and animal models of AD. Despite its apparent intraneuronal localization early in the disease-process, studying the occurrence and pathological relevance of iAβ has been confounded by much controversial debate: antibodies targeting Aβ peptides typically show specificity for the amyloid precursor protein (APP), which is physiologically abundant in the neuronal space. Using a highly specific Aβ-directed antibody and super-resolution microscopy, we show that neurons within the control-human hippocampus carry appreciable amounts of detectable intraneuronal Aβ-immunoreactive material, and that these immunoreactive sites are distinguishable from those associated with APP; co-localization analysis reveals that over 90% of Aβ-immunoreactive sites are spatially distinct from those associated with APP. We further test the specificity of our antibodies by peptide-adsorption. Our results validate the occurrence of iAβ, implicating the toxic intracellular material as an early feature of the asymptomatic phase of AD.

2-C -95 Motor-Unit Specific Alterations of Synaptic Plasticity at the NMJ and Neuromuscular Function in an ALS Mouse Model

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Background. Amyotrophic lateral sclerosis (ALS) is a late-onset neurodegenerative disease characterized by the progressive loss of motoneurons. In ALS, motor units (MU) appear differentially susceptible to denervation: fast fatigable (FF) MU are the most vulnerable and slow (S) MU the most resistant. Objectives. We hypothesized that the MU selective vulnerabilities observed in ALS will be associated with MU-specific NMJ alterations of synaptic strength and plasticity. Methods. Electrophysiological recordings were performed on ex vivo nerve-muscle preparations of the fast-twitch Extensor Digitorum Longus (EDL; FF MU) and the slow-twitch Soleus muscles (SOL; S and fast fatigue resistant, FR MU) of the SOD1G37R mice and their WT littermates. Asymptomatic (P180), pre-onset (P380) and disease onset (P450) stages were studied. Muscle contractions were induced by motor nerve or muscle stimulation and monitored using a muscle force transducer. Results. The quantal content of S MU was increased while FF MU from SOD1 mice was decreased compared to WT mice. Long-term synaptic plasticity was also altered as a function of MU type such that synaptic depression was significantly enhanced in SOD1 FF NMJs. However, in the SOL, synaptic plasticity was only reduced after disease onset in FR MU. Muscle strength was significantly decreased from P380 in the mutant SOL, but a higher resistance and a better recovery to fatigue was observed at P450. Conclusions. As a whole, these results reveal that NMJ function is differentially altered according to MU susceptibility in ALS.

2-C -96 Altered neural complexity in Schizophrenia: Combined insights from resting-state MEG and machine learning

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Complex systems, such as the brain, often exhibit temporal fluctuations characterized by a 1/f-like scaling (He, 2014). A useful framework to quantify scale-free temporal and spatial properties of neural activity is through multifractal analysis. While this approach has been applied to certain physiological phenomena, (e.g. cardiac signal) it is still emerging in psychiatry. Recently, neuroimaging studies have shown that neural complexity is altered in pathologies, such as schizophrenia (SZ) (e.g., Fernandez et al, 2013). In this study, we further explored changes in scale-free dynamics in SZ using resting-state magnetoencephalography (RS-MEG) and machine learning. Five minutes of RS-MEG was recorded in 25 SZ patients and 25 healthy controls. Analyses were conducted using the Wavelet Leader-based Multifractal formalism (Wendt et al, 2007) to measure scaling parameters, such as C1 (measure of self-similarity) and C2 (measure of multifractality). Detrended fluctuation analysis was also used to measure long-range temporal correlation across various frequency bands, along with Hurst exponent and permutation entropy. Permutation tests with maximum statistics correction applied to the features revealed significant differences in neural complexity between the two groups. This was followed-up with machine-learning classification to identify the most discriminant - SZ related - scaling parameter. Statistical significant decoding accuracies of over 70% were measured for some scaling metrics. The findings of this study could help reveal a new type of biomarker for early SZ diagnosis.

2-C -97 Effects of developmental ethanol exposure on the physiology and morphology of medial prefrontal layer VI neurons in young postnatal and adolescent mice.

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Exposure to ethanol during development can lead to teratogenic outcomes in humans that manifest as Fetal Alcohol Spectrum Disorder (FASD). This includes persistent deficits to cognitive processes including attention. We have shown previously that developmental ethanol exposure impairs attention in adult mice, and alters the physiology and morphology of pyramidal neurons located within layer VI of the medial prefrontal cortex (mPFC) that support this cognitive function. The goal of this current study was to determine whether these developmental ethanol-induced alterations to mPFC layer VI neurons are also present early in postnatal life, which may identify these neurons as a potential target for early intervention. Developing mice were exposed to binge-like ethanol treatment or air (control) using vapour chambers from gestational days 10 to 18 (term, 19 days) and from postnatal days (P) 4 to 14. Electrophysiological analysis of mPFC layer VI pyramidal neurons at P15 and P25 reproduced known effects of age and sex on neuron physiology in control mice. However, these experiments found developmental ethanol treatment to increase nicotinic acetylcholine responses for female mice only, suggesting that altered nicotinic signaling following developmental ethanol exposure varies by sex and occurs earlier in females. Since developmental ethanol exposure and nicotinic signaling can influence mPFC layer VI neuron growth and maturation, ongoing experiments are investigating the morphology of the same mPFC layer VI neurons that were tested in the electrophysiological experiments.

2-C -98 MNK1 Inhibition Is Neuroprotective Against MAPK-Mediated Injury Via eIF4E Dependent Translation

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Mechanisms underlying neurodegeneration in response to metabolic and excitotoxic stress are still not completely understood, and no treatments effectively target this damage. A small molecule screen by our group identified MNK1 (MAP kinase interacting serine/threonine-protein kinase 1) as a potential target for this injury. MNK1 regulates protein translation through Eukaryotic Translation Initiation Factor 4E (eIF4E), in response to stress and inflammation. MNK1 is itself activated by ERK and p38 Mitogen Activated Protein Kinases (MAPKs). The role of MNK1 has not been well explored in neurodegeneration. Yet, ERK and p38 MAPKs, and proteins regulated by eIF4E, have been closely implicated. We hypothesized that MNK1 contributes to neurodegeneration downstream of MAPK signaling by modulating eIF4E-dependent translation. Using the MNK1 inhibitor CGP57380, we confirmed that neuronal cell viability was significantly rescued from glutamate injury, in a dose dependent manner, compared to vehicle. Similarly, inhibition of eIF4E using the antagonist 4E1RCat also resulted in rescue. Interestingly, ERK, but not p38, inhibition was protective, and both CGP57380 and 4E1RCat blocked cell death induced by ERK activation. Finally, we demonstrated in vivo that increasing concentrations of CGP57380 protected mouse retinal ganglion cells (RGCs) from excitotoxic injury compared to vehicle. This study provides evidence that an ERK-MNK1-eIF4E signalling pathway may be a novel therapeutic target for excitotoxic and metabolic injury in retina and related neurodegenerative processes.

2-C -99 A Rat Model of Hyperphosphorylated Human Tau in the Locus Coeruleus: Capturing the Initiating Pathological Progression of Sporadic Alzheimer?s Disease as Proposed by Braak

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Braak proposes that Alzheimer's Disease (AD) begins with hyperphosphorylated soluble tau in the locus coeruleus (LC) which, over decades, spreads along LC axons to other structures via a prion-like process. In a rat model, we use a viral vector carrying the full human tau gene (htau), pseudophosphorylated at 14 sites hyperphosphorylated in AD and containing a DIO component to limit its expression to tyrosine

hydroxylase (TH)-producing neurons in TH-Cre rats. Htau was linked to an enhanced green fluorescent protein (GFP). The vector was directed at LC and gene expression visualized by fluorescence microscopy. There was good LC expression, with some rats showing sub-coerulear or, with anterior infusions, ventral tegmental area expression. GFP was seen in the somatodendritic compartment (pretangle stage 1) and in LC axons. Spread in LC axons was consistent with tau transport. Evidence of extracellular co-secretion of htau and dopamine-beta-hydroxylase (DBH) was seen by12 weeks post LC-infusion. Neuronal activity is associated with vesicular secretion of DBH and tau, but co-secretion has not been reported. DBH/htau inclusion entities, ranging from `~10-60 square microns in area, appeared adjacent to DAPI-stained nuclei. Inclusions occurred in areas of LC innervation including cerebellum, the pontine nuclei, hippocampus and olfactory bulb and varied in size by structure and time post-infusion. Spatially inclusions were most numerous adjacent to projection neurons: cerebellar Purkinje cells, hippocampal CA3 pyramidal cells, bulbar mitral cells and among the pontine neurons.

2-C -100 Role of TRPM7 in glioblastoma cellular functions

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Glioblastoma (GBM) remains the most common and aggressive malignant brain tumor originating in the central nervous system. Diagnosis is lethal with a median survival of <15 months. Aberrant TRPM7 expression has been linked to GBM cellular functions. Here, using the human GBM cell line U87, we further established TRPM7 as a potential therapeutic target by evaluating the TRPM7 potentiator, naltriben, on GBM viability, migration, and invasiveness. Firstly, with the whole-cell patch-clamp technique, we demonstrated that naltriben enhanced the endogenous TRPM7-like current in U87 cells. With Fura-2 Ca2+ imaging, we showed robust Ca2+ influx following naltriben application. U87 cell migration and invasion (assessed with scratch wound assays, Matrigel invasion experiments, and MMP-2 protein expression) were significantly enhanced with naltriben, but not viability and proliferation (evaluated with MTT assays). With Western immunoblots, we also assessed the protein levels of p-Akt/t-Akt, and p-ERK1|2/t-ERK1|2. We found that, in U87, naltriben enhanced the MAPK/ERK signaling pathway, but not the PI3k/Akt pathway. Therefore, potentiated TRPM7 activity contributes to the devastating migratory and invasive characteristics of GBM.

2-C -101 HUMAN NEURONS AND ASTROCYTES EXPRESS NKG2D LIGANDS AND ARE SUSCEPTIBLE TO NKG2D-MEDIATED KILLING

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Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS). Our group has identified NKG2D as a potential key player in MS pathobiology. NKG2D is an activating co-receptor expressed by several subsets of immune cells including CD8 T cells. In humans, it binds to various ligands (NKG2DL), including MICA, MICB and ULBP (1-6) which are induced by environmental triggers such as inflammation. We have previously shown that human oligodendrocytes express NKG2DL in vitro. Blockade of NKG2D inhibits the killing of oligodendrocytes by human immune effector cells. Moreover, our group detected MICA/B in MS lesions, however, other NKG2DLs have not been investigated. We hypothesize that human neurons and astrocytes exposed to inflammatory conditions also upregulate NKG2DL and consequently become susceptible to NKG2D-mediated killing by activated CD8 T cells. Our goal is to characterize the expression of NKG2D and its ligands and the impact of such expression in MS patients. We observed that primary cultures of human neurons and astrocytes express the ligand ULBP4. However, only astrocytes upregulate this expression in the presence of cytokines such as TNF and IFNγ.

Moreover, in vitro NKG2D blocking diminishes astrocyte and neuronal death mediated by human immune effector cells. Our results suggest that not only oligodendrocytes but also human neurons and astrocytes, can be susceptible to NKG2D-mediated killing. We are currently investigating the expression of NKG2DL in MS and control brains to determine their role during this inflammatory neuropathology.

2-C -102 Emotion recognition in pediatric brain tumor patients: viewing patterns and white matter structure

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Introduction: Pediatric brain tumor survivors display emotion recognition deficits, and eye-movement monitoring might help explain why. Successful emotion recognition is thought to rely on white matter (WM) that connects occipital to anterior brain regions. Thus, we examined if emotion recognition deficits are related to viewing patterns and to occipital WM. Methods: 10 patients treated for posterior fossa brain tumors, and 4 healthy children participated in this study at SickKids (Toronto, Ontario). The Diagnostic Analysis of Nonverbal Accuracy (DANVA-2), a facial emotion recognition task, was administered while eye-movements were recorded. Diffusion tensor imaging (DTI) was used to assess fractional anisotropy (FA). Occipital FA, and regions where FA differed between groups, were correlated with emotion recognition ability. Results: Patients made more emotion recognition errors than controls ($p=0.04$); however, groups didn't differ in the number of fixations made on, or in the time(ms) spent looking at, the faces (all $p>0.05$). Patients had lower FA than controls in the vermis ($p=0.001$) only. Across all participants, FA was negatively correlated with the number of incorrect responses in the occipital region ($r= -0.63$, $p=0.03$), and vermis ($r= -0.64$, $p=0.03$). Conclusion: We confirmed emotion recognition deficits in our brain tumor sample, yet inattention to the faces does not appear responsible. Occipital and vermal WM may be important for effective communication between posterior and anterior brain regions in order to facilitate successful emotion recognition.

2-C -103 Limbic grey matter alterations in patients with trigeminal neuralgia

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Objective: Trigeminal neuralgia (TN) is a chronic disorder characterized by sudden shock-like pain of the face. A prior study showed gray matter (GM) abnormalities in TN patients in areas associated with pain perception and emotion, such as the thalamus and amygdala (DeSouza et al, 2013). We aimed to explore possible changes to other major limbic, or affect-related, areas including hippocampus, nucleus accumbens, insula, and cingulate. Methods: 47 patients and 62 healthy people were scanned using a 3T GE Signa HDx MRI scanner and an 8-channel head coil were used to acquire T1-weighted 3D FSPGR images. Freesurfer software (v. 4.5.0) was used for brain imaging, and SPSS for statistical, analyses (v. 22). Results were corrected for multiple comparisons ($p < 0.05$). Results: Patients and controls differed significantly in GM volumes in all areas of the affective circuitry studied (i.e. hippocampus, accumbens, insula, and mid and posterior cingulate). Unilateral differences were noted for patients with right- (R: 2067 mm3; L: 2681 mm3) vs. left- (R: 2009 mm3; L: 2296 mm3) sided pain in the rostral anterior cingulate compared to controls (R: 2228 mm3; L: 2740 mm3). There were no differences noted for the isthmus of the cingulate. Conclusion: Decreased GM volume was noted throughout affect-related circuits, with rostral anterior cingulate changes possibly related to the side of pain. These changes could reflect the negative affective experiences and brain function commonly associated with chronic pain sufferers and may be used in future to assist in clinical prognosis.

2-C -104 Reduction of the cholinergic innervation of the subthalamic nucleus in Parkinson's disease

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The subthalamic nucleus (STN) exerts a major glutamate-mediated excitatory influence upon several key structures of the basal ganglia. In turn, the STN neuronal activity is modulated by multitudinous chemospecific afferents, including a cholinergic (ACh) input that originates from the brainstem pedonculopontine tegmental nucleus (PPN). Neurons of the STN are hyperactive in Parkinson?s disease (PD) and their silencing through chronic deep brain stimulation significantly improves motor behaviour in PD patients. Neuropathological studies have documented a significant degeneration of PPN neurons in PD, but the reflection of such neuronal degeneration upon the PPN target structures has not yet been investigated. Because of its crucial role in basal ganglia functioning, the STN was examined to see if its ACh innervation is altered in PD patients. We used antibodies raised against choline acetyltransferase (ChAT), the synthesis enzyme of ACh, to visualize ACh neuronal structures in the post-mortem human STN. The density of ChAT-immunolabeled axon varicosities was estimated by an unbiased stereological approach. Our preliminary results obtained in the whole STN reveal a 97% decrease of the ACh innervation of the STN in PD (6,900 ChAT+ axon varicosities / mm^3 of tissue) compared to age-matched control (290,000 ChAT+ axon varicosities / mm^3). Such a marked reduction of the ACh innervation is likely to significantly contribute to the development of STN hyperactivity and the ensuing basal ganglia dysfunction that characterize the PD state.

2-C -105 Diffusion-Weighted MRI Identifies Brain Regions Affected by Spreading Depression during Fatal Seizures

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Spreading Depression (SD) is a neurophysiological phenomenon of long-lasting neuronal inactivity that follows a large-scale depolarization of brain cells. SD propagates through the brain at approximately 3-5 mm per minute causing an underlying swelling in the brain tissue invaded. This swelling alters the average diffusion properties of water in brain parenchyma, which we have utilized to visualize SD across the entire brain with Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI). Combining DW-MRI with EEG monitoring and brain stimulation we have examined the propagation of SD during fatal and non-fatal seizures in a mouse model of Sudden Unexpected Death in Epilepsy (SUDEP). SD induced by non-seizure causing brain stimulation is generally constrained to the cortex, occasionally penetrating the striatum and hippocampus. Conversely, stimulation that triggers non-fatal seizures result in SD that also invades the thalamus and inferior colliculus that we hypothesize act as "gate" regions to further SD propagation. Finally, during fatal seizures SD further invades the brainstem, which may relate to the cardio-respiratory failure that occurs during fatal seizures. In addition to whole brain in vivo imaging we have targeted the thalamus and inferior colliculus for whole-cell patch clamp in acute brain slices. Examining intrinsic excitability and synaptic activity we define the neuronal correlate(s) for hyperexcitability in the hypothesized SD "gate" regions.

2-C -106 Impact of aging in the evaluation of neuroprotection and immunomodulation of the enteric nervous system in the MPTP mouse model of Parkinson's disease

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Parkinson's Disease (PD) is characterized by motor symptoms generally preceded by gastrointestinal dysfunctions, resulting from the alteration of dopamine (DA) neurons in the myenteric plexus (MP). Previously, we demonstrated the major contribution of pro-inflammatory response in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced toxicity on enteric DA neurons. The aim of this project was to evaluate the impact of aging on gut neuroprotection and immunomodulation in a MPTP model of PD. Adult male NFκB-eGFP mice received 4 intraperitoneal injections of saline or MPTP (8 mg/kg) at 2 hrs intervals. Five or ten days later, mice were killed, the ileum was fixed and microdissected to isolate the MP. Immunofluorescences with tyrosine hydroxylase (TH) and ionized calcium-binding adapter molecule 1 (Iba1) antibodies were performed for counting of DA neurons (TH+) and macrophages (Iba1+). Our preliminary results revealed that TH neuron and macrophage densities were respectively decreased and increased in young MPTP mice (about 100-day-old), as already shown in our previous studies. Strikingly, in saline condition, we found that the older the mice were, the more TH neuron density decreased and the more inflammation increased. To the same extend as old control mice (about 300-day-old), old MPTP mice exhibited low densities of TH neurons and high densities of macrophages, suggesting that the pool of MPTP-sensitive DA neurons was already lost by aging. Consequently, in clinical studies, the age of patients could potentially influence the interpretation of MP analysis.

2-C -107 Characterization of a Non-Human Primate Model of Alzheimer's Disease

Susan Boehnke[1], Robert Wither[1], Joseph Nashed[1], Ann Lablans[1], Brian Coe[1], Andrew Winterborn[1], Sergio Ferreira[2], Douglas Cook[1], Ron Levy[1], Fernanda De Felice[2], Douglas Munoz[1]
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We recently developed a non-human primate (NHP) model of Alzheimer's Disease (AD) that recaptitulates key molecular aspects of human pathology (Forny-Germano et al.,J.Neurosci,2014). AD pathology was induced via intracerebroventricular (icv) injection of neurotoxic amyloid beta oligomers (AßOs). We are now tracking disease progression in vivo in male rhesus macaques receiving either 1) icv injections of AßOs (100-400µg) approximately once per month for 12-18 months; or 2) a sequence of smaller (~80ug) icv injections 3x per week for 3 weeks. To track behavior we used an activity tracker and 24/7 video. To measure cognition we used a cage-side touch-screen device with cognitive tasks from the CANTAB AD battery. To track synaptic degradation we analyzed resting state functional connectivity via fMRI. To track molecular biomarkers in the CSF we quantified Aß1-40, Aß1-42, Tau, pTau, cytokines and neurofilament light chain. Blood biomarkers were also tracked. We observed spatial working memory deficits (spatial span task), and an inability to learn new tasks (delayed match to sample and paired associates learning) following injections. Reductions in resting-state functional connectivity were also observed among memory-related areas. Changes in Aß with injections could be tracked in the CSF, along with an increase in pTau. The long-term goal is to relate these in vivo metrics to each animal's post-mortem brain pathology. Overall, we validate a viable platform to evaluate AD-like features in primates, which could easily be translated to other primate models of neurodegeneration.

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2-C -108 Expression and proteomic analyses of kif1a/25b in hereditary sensory and autonomic neuropathies type II

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Hereditary sensory and autonomic neuropathies form a group of genetic disorders characterized by variable sensory and autonomic dysfunctions. HSAN type II (HSANII) is a debilitating subtype manifesting in early childhood with distal numbness and loss of pain, temperature and touch. Our laboratory has reported truncating mutations in a nervous-tissue-specific exon (HSN2) of the WNK1 gene. The WNK1 isoform containing the alternatively spliced exon (HSN2) is referred to as the WNK1/HSN2 isoform. Interestingly the protein region encoded by the alternatively spliced exon was found to interact with a particular isoform of another HSANII causative gene, KIF1A. The HSANII-causing KIF1A isoform is referred to as KIF1A/25B since disease-causing mutations were exclusively found in the alternative exon ?25B?. The expression profile of KIF1A/25B across the nervous system is determined by performing WB immunodetection using tissues from wild-type mice and a rabbit antiserum. The function of the protein encoded by exon 25B is assessed through a profiling of its interacting partners by performing co-immunoprecipitation for both full-length KIF1A/25B protein and the protein that correspond to exon 25B. Positive interactions are confirmed using liquid chromatography?mass spectrometry. I hypothesize that KIF1A/25B is the transit system through which WNK1/HSN2 traffics within the cells and offers the two proteins an opportunity to interact with other cellular elements relevant to the sensory and nociceptive aspects of HSANII.

2-C -109 Precocious myelination in a mouse model of autism

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Autism spectrum disorder (ASD) is a neurodevelopmental disease, which has been hypothesized as a result of altered connectivity in the brain. Imaging studies have found increased functional and structural connectivity in young children with ASD, while they are generally reduced in adolescents and adults with the condition. Myelin is an integral part of white matter and critical for connectivity; however, its role in ASD has not been well studied. Here, we investigated myelin development in a

behaviorally robust model of ASD, the BTBR mice. We found that myelination in both male and female BTBR pups was accelerated, indicated by increased expression of myelin-specific proteins and appearance of mature oligodendrocyte in corpus callosum, caudate putamen, and frontal cortex, compared with age-matched B6 control mice. However, relative thickness of myelin was similar in adult mice, suggesting that increased myelination was transient and developmental. Supportive of these results, we also found that expression of platelet-derived growth factor receptor alpha (PDGFRA), which is a specific marker of oligodendrocyte precursor cells (OPCs) and a key molecule in determining the timing of OPC differentiation, was reduced in the brain of BTBR pups. Meanwhile, the number of OPCs and the level of PDGF-A was unaltered, suggesting overall decreased PDGFRA signaling in OPCs. Together, these results revealed precocious development of myelin in the BTBR model of ASD, involving altered PDGFRA pathway. These changes could be a basis of increased connectivity observed in young children with ASD.

2-C -110 The effectiveness of the Anti-CD11d treatment is reduced in rat models of spinal cord injury that produce significant levels of intraspinal hemorrhage

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Neurological outcomes of rats and mice after clip compression spinal cord injury (SCI) are improved by acute treatment with a monoclonal antibody against the CD11d subunit of the CD11d/CD18 integrin expressed by neutrophils and monocyte/macrophages. However, the limited effects of anti-CD11d treatment in a study by Hurtado et al. (2012) suggest that severity and type of lesion may play an important role in the success of the treatment. To investigate this idea, we tested the anti-CD11d treatment in two models of contusion SCI and compared our results to treatment effects after clip-compression SCI. One study, executed at the International Collaboration on Repair Discoveries in Vancouver, BC tested the mAb in a cervical hemi-contusion model of rat SCI and the other, conducted at the Robarts Research Institute in London ON, tested the mAb in a contusion model of SCI at the 12th thoracic spinal segment of rats. Our analyses of locomotor recovery, intraspinal oxidative damage, inflammation and hemorrhage in anti-CD11d-treated and control rats provides evidence that the anti-CD11d strategy is most effective in instances where frank hemorrhage into the injured spinal cord is minimal. This suggests that the beneficial effect of the CD11d mAb treatment depends on the type of SCI under investigation, and requires that active leukocyte diapedesis be a major contributor to the pathophysiology triggered by the injury for its anti-inflammatory efficacy.

2-C -111 Sex Matters: Repetitive Mild Traumatic Brain Injuries are Associated with Behavioural, Epigenetic, and Structural Changes in Adolescent Rats

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[1]The Florey Institute of Neuroscience and Mental Health, [2]Alberta Children?s Hospital Research Institute

Mild traumatic brain injury (mTBI) is a common form of neurological insult in adolescence, with exposure to repeated mTBIs (RmTBI) increasing the risk of lingering symptomology (i.e., postconcussion syndrome; PCS). There is no effective process for distinguishing between those that will develop PCS and those that will not. There is also a void in the literature with respect to how the female brain is affected by mTBI. Therefore, we utilized an innovative modeling platform to induce mTBIs that mimic sports-related concussion and examined the behavioural, epigenetic, and structural brain changes associated with mTBI and RmTBI in adolescent rats of both sexes. Behavioural changes were assessed with a test battery previously demonstrated to evaluate symptomology consistent with PCS. Changes in corpus

callosum (CC) and prefrontal cortex (PFC) expression of GFAP, MBP, NFL, and Tau were examined. Structural changes within the CC and PFC were assessed with volumetric and diffusion magnetic resonance imaging (MRI). We found sex differences in behavioural and epigenetic outcomes, which are consistent with literature regarding PCS. Interestingly, RmTBI resulted in sex-specific changes on MRI outcomes, with females having reduced PFC volume on structural MRI (i.e., a marker of atrophy) and males having diffusion MRI changes in the CC (i.e., a marker of axonal injury). These findings suggest that the sex differences in the behavioural manifestations associated with PCS following RmTBI in this model may be associated with sex-dependent changes in brain structure and gene expression.

2-C -112 Decreased mitochondrial cyclic AMP response element-binding protein (CREB) level in the cortex of 3xTg mice coincide with mitochondrial impairment

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[1]University of Manitoba, [2]St. Boniface Hospital Research , [3]St. Boniface Hospital Research

Alzheimer's disease (AD) is characterized by progressive neuronal loss, especially in the cortex and hippocampus, and mitochondrial dysfunction was proposed to be an early event in the onset of AD. Here, we attempt to describe dysfunctional processes in brain mitochondria of 3xTg AD mice, by analyzing their function and morphology (fission and fusion). We further try to relate it to the alterations in mitochondrial CREB, since it is established that CREB mediates mitochondrial gene expression and neuronal survival. Cortical mitochondria of 3xTg and control mice, 6 month-old, were analyzed for Complex I-dependent oxygen consumption rates (OCR) on the Seahorse XF24 Analyzer and Complex II-dependent OCR on Oxygraph 2K (Oroboros) instruments. Western blotting was used to determine protein levels of selective Complex I-V subunits, mitofusin 2 (Mfn2) and dynamin-related protein 1 (Drp1) and mitochondrial CREB. We found that coupled and maximal respiration were significantly decreased in cortical mitochondria from female 3xTg mice (*$p<0.05$, n=5). In males, only maximal respiration was down. Western blot results revealed significant decreases in Complex I and Complex IV protein levels in the cortical mitochondria of 3xTg females, but not in males. Decreases in Mfn2 protein level in the cortical mitochondria from both female and male 3xTg coincided with an increased level of Drp1. Significant decreases in mitochondrial CREB most likely contribute to the mitochondrial deficits in function and morphology, leading to neuronal loss associated with neurodegenerative disorders.

2-C -113 Altered Intrinsic firing of Purkinje Cells in a mouse model of ARSACS

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[1]McGill University

The autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), an early onset neurodegenerative disease, is caused by mutations in the SACS gene encoding the protein sacsin. A major symptom of ARSACS is cerebellar ataxia characterized by the progressive loss of Purkinje cells in the anterior lobes of the cerebellum. We use SACS knockout (Sacs-/-) mice model, which develop progressive motor deficits and neuronal abnormalities resembling those of ARSACS patients. We observed that Purkinje cell firing was reduced in postnatal day (P)40 in Sacs-/- mice compared to litter-matched control mice (WT) and as early as P20, prior to the detection of motor phenotypes (WT: 85 ± 3.3 Hz, n=31 cells; Sacs-/-: 70 ± 3.7 Hz, n=38 cells; $p<0.005$). To determine if the changes in firing rate were due to changes in the intrinsic properties of Purkinje cells we performed whole cell recordings at P40. We found no differences in the spike shape (height, width or after-hyperpolarization amplitude) of evoked action potentials between Sacs-/- and WT animals (WT n=13; Sacs-/- n=15; $p>0.05$). Step current injections show that the maximal instantaneous frequency is not affected in Sacs-/- mice (WT: 347 ± 19

Hz, n=10 cells; Sacs-/-: 312 ± 11 Hz, n=13 cells; p=0.13) although Sacs-/- Purkinje cells fail to sustain firing at high current steps (maximal frequency over 500 ms of current injection: WT: 276 ± 24 Hz, n=10 cells; Sacs-/-: 194 ± 17 Hz, n=13 cells; p<0.05). This suggests that alterations in either cell energetics or ion channels involved in sustain-firing could contribute to Purkinje Cells

2-C -114 Striatal histone acetylation is modulated by dopamine depletion in the MPTP-induced mouse model of Parkinson's disease.

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Parkinson's disease (PD) is a chronic progressive neurodegenerative movement disorder characterized by a selective loss of nigrostriatal dopamine (DA) neurons. The molecular adaptation of striatal neurons to DA deficiency remains poorly understood. Acetylated and deacetylated histones are considered epigenetic tags within chromatin by increasing or decreasing gene transcription levels. In the present study, we verify whether acetylation of histone play a role in the molecular adaptation of striatal neurons and the impaired motor behavior associated with DA depletion. The neurotoxin MPTP was acutely administered to adult mice using 4 injections of 20 mg/kg, i.p., every 2 hours. Mice were sacrificed 1 or 7 days after MPTP injections. To evaluate motor manifestations, we performed 7 days after treatments the wire suspension and pole tests in vehicle and MPTP-treated mice. Statistical significance was reached only in the wire test. Degrees of DA-depletion were estimated by the evaluation of tyrosine hydroxylase (TH) levels in the striatum using western blot technique. We observed a 45% and a 60% reduction in striatal TH levels in mice sacrificed 1 and 7 days after MPTP injections, respectively. Modification of histone acetylation was assessed in the striatum of mice following MPTP treatments and elevated levels of lysine 9-acetylated histone H3 (H3K9ac) were observed in MPTP mice 7 day after injections with statistical significance. These preliminary results indicate that DA depletion triggers epigenetic modification of histone proteins in the striatum of MPTP-treated mice.

2-C -115 Alterations to the NGF metabolic cascade in human AD and MCI

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A novel pathway has been shown to control the extracellular production of Nerve Growth Factor (NGF) from proNGF and the degradation of mature NGF (Bruno and Cuello, PNAS, 2006). Basal forebrain cholinergic neurons depend on NGF (Hefti, 1986); dysregulation of the NGF metabolic pathway in Alzheimer's disease (AD) could therefore lead to cognitive impairments, as the cholinergic system is critical for cognition (Davies and Maloney 1976, Bowen et al. 1976, Mesulam, 2004). Using human brain samples from the Religious Orders Study (RUSH Memory Clinic, Chicago), we fully analyzed the NGF metabolic pathway in AD and MCI (a potential precursor to AD) using Western Blot, ELISA, and qPCR. We observed an upregulation of proNGF protein with no change in mRNA. While plasmin, the convertase responsible for the maturation of proNGF, could not be assessed due to its transience, we observed a build-up of plasminogen protein (but not mRNA), suggesting impaired activation of plasmin from its zymogen. While ELISA revealed no change in the plasmin activator tPA, the CNS inhibitor of tPA, neuroserpin, showed greater protein levels in AD and MCI, and greater mRNA expression in MCI. The metalloproteases MMP3 and MMP9, which degrade mature NGF, were upregulated as protein and mRNA in both MCI and AD. This pattern of dysregulation is consistent with a reduction in the maturation of NGF and an increase in its degradation. The dysregulation of the NGF metabolic pathway may

therefore contribute to cholinergic deficits in MCI/AD and may provide new opportunities for therapeutic intervention.

2-C -116 EFFECTS OF AEROBIC EXERCISE ON NEUROPLASTICITY IN SUBJECTS WITH NEUROLOGICAL DISEASES: A SYSTEMATIC REVIEW

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Background: Neuroplasticity is an important mechanism of recovery after neurological injury. Animal studies indicate that aerobic exercise can improve neuroplasticity. Aim: To perform a systematic review about the efficacy of aerobic exercise on neuroplasticity in subjects with neurological diseases. Methods: The PRISMA guidelines were followed. A search of clinical trials was performed on MEDLINE and PEDro databases, without language or date restrictions. Two independent reviewers screened all the studies, and extracted data. Trials' quality was assessed by the PEDro scale. Results: The median PEDro score of the trials was five. Out of the eight studies included in the review, three included participants with parkinson's disease (37.5%), three with multiple sclerosis (37.5%), one with stroke (12.5%) and one with spinocerebellar ataxia (12.5%). Neuroplasticity measures were different between the studies, including molecular regulators of neuronal plasticity (50%), corticomotor excitability (25%), expression of the dopamine D2 receptor (12.5%), and disynaptic reciprocal inhibition and D1 inhibition tests of the soleus and tibialis muscles (12.5%). The majority of the studies showed the efficacy of aerobic exercise in improving neuroplasticity (87.5%). Conclusions: Few clinical trials assessed aerobic exercise effects on neuroplasticity in subjects with neurological diseases. The results were positive about the improvement of these outcomes. Further studies are necessary to confirm the efficacy of aerobic training on neuroplasticity in subjects with neurological disorders.

2-C -117 RHBDL4-mediated APP processing - novel insights into APP physiology?

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The physiological functions of the amyloid precursor protein (APP), regarded as one of the key players in Alzheimer disease (AD), assemble around cell-matrix and cell guidance pathways, but have not been resolved in full detail to date. APP undergoes amyloidogenic processing by beta- and gamma-secretase leading to the secretion of toxic amyloid-beta (Abeta) peptides. Further, increasing levels of Abeta peptides can be detected up to 20 years before any clinical symptoms of Alzheimer disease occur. Thus, one of the most common strategies to prevent or halt the disease progression is to lower Abeta levels. Besides gamma-secretase, rhomboid proteases form another conserved class of intramembrane proteases, which cleave their substrates within transmembrane and ectodomain regions. Despite their high degree of conservation, only a couple of substrates for human rhomboid proteases are known so far. We now found that the human rhomboid RHBDL4 efficiently cleaves APP in vitro at least at 7 different sites within the ectodomain, generating novel APP fragments inside the cell. Importantly, RHBDL4-mediated APP processing prevented the generation of Abeta peptides. Further, knockdown of RHBDL4 using shRNAs resulted in a decrease of endogenous APP fragments indicating that RHBDL4-mediated APP processing is physiologically relevant. We are currently investigating the membrane composition as a mediator of RHBDL4-APP interactions and regulator of RHBDL4 activity. In summary, we are characterizing a novel APP processing pathway, that might prove therapeutically relevant for AD.

2-C -118 Investigating the impact of midlife obesity on Alzheimer's disease pathology

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Midlife obesity is a significant risk factor for Alzheimer's disease (AD). Studies have supported that obesity accelerates AD-related pathology and memory impairment in mouse models of AD. To elucidate the relationship between midlife obesity and AD-related neuropathology, we evaluated the impact of midlife obesity on the brain morphology of the triple transgenic mouse model of AD (3xTg; harbouring mutations leading to both amyloid and tau accumulation) using longitudinally acquired magnetic resonance imaging (MRI). At 2 months of age, animals were placed on a high-fat diet (HFD; n=3) or an ingredient equivalent control diet (CD; n=5). Animals were scanned with MRI at 2 months, 4 months (midlife), and 6 months. The MAGeT Brain algorithm was used to segment the MR images using a multi-label voting procedure, resulting in segmentations for 159 structures per hemisphere. A linear mixed effects model was used to assess volumetric changes in MRI-derived brain morphology. We observed a significant effect for the diet by time point interaction, driven by decreases in the bilateral hippocampus (right t=-4.55; left t=-2.59) and fornix volumes (R t=-3.32; L t=-2.23), increases in bilateral lateral ventricle volumes (R t=-3.29; L t=-2.59), and a decrease in the right caudomedial entorhinal cortex (t=-2.44) ($p<.05$ for all). Our results suggest that midlife obesity may accelerate the brain atrophy associated with AD-related pathology in the 3xTg mouse model. Further insight into this process may have significant implications in the development of lifestyle interventions for AD.

2-C -119 Investigating the role of MYO9B in cortical GABAergic interneuron development in epileptic encephalopathies

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Epileptic encephalopathies are early onset conditions characterized by refractory seizures and developmental delay often associated with poor prognosis. In a previous WES study, we identified a de novo mutation in the MYO9B gene in a patient with sporadic EE.MYO9B encodes the unconventional myosin involved in maintenance of cell shape and motility. Myo9b controls dendritic patterning of pyramidal cells, but its role in interneurons (INs) is unknown.As GABAergic INs play key role in the regulation of cortical excitability, we hypothesized that deficiency of Myo9b may result in disturbance of cortical IN network.We investigated the impact of Myo9b knockdown in vitro in MGE derived INs using shRNA-based electroporation and discovered significant morphological alterations in migrating INs with elongated leading processes.To further investigate the role of Myo9b in developing INs,we conditionally deleted the gene in mouse MGE INs using the Nkx2.1-Cre driver.Although the number of inhibitory INs was unchanged in the somatosensory cortex of the Nkx2.1Cre; Myo9bloxP/loxP mice,these mutant mice display increased anxiety and impairment in spatial and reversal learning abilities,suggesting a possible disruption of limbic and cortical network inhibition.Ongoing experiments will characterize the impact of Myo9b deletion on IN migration dynamics using time-lapse confocal imaging,as well as on their synaptic function using in vitro electrophysiology.Together,our data provide insights into the key roles of MYO9B in regulating cortical INs development and its possible involvement in EE.

2-C -120 TrkA as a pharmacological target to modulate memory formation

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Cognitive impairment in aging is associated with a phenotypic and functional decrease of the receptor TrkA for NGF. Compound D3, a partial agonist for TrkA, rescues memory in animal models of cognitive impairment. Paradoxically, D3 induces persistent cognitive deficits in WT mice. We hypothesize that this deficit is due to a disruption of homeostasis in the normal hippocampal circuitry; we expect excess activation of trophic pathways downstream of TrkA activation to lead to an impairment in memory consolidation. Our overall objective was to study the pharmacodynamics of D3 in order to elucidate TrkA-associated mechanisms of memory formation. The effect that acute intraventricular administration of D3 has on the memory of WT mice was characterized by behavioral analysis, looking at short and long term memory pertaining to the hippocampal-based spatial memory, recognition-based short and long term memory, as well as learning abilities in the mice. We were able to confirm that the WT, D3-treated mice show impairment in spatial memory, in comparison to the WT controls. In addition, we determined that D3 affects memory consolidation. Subsequently, the brains were retrieved for biochemical analysis and neurons were phenotyped. Our results indicate variations in important molecular pathways in the hippocampus and nucleus basalis, including the Akt and MAPK pathways. This study provides a new approach to study the importance of TrkA receptors in the process of memory formation, by studying the effect of acute administration of D3, a partial agonist of the TrkA receptor for NGF.

2-C -121 Sex-Specific Transcriptional Signatures in Human Depression

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In this study, we provided a comprehensive molecular description of the transcriptional signatures associated with MDD in males and females and defined some of the molecular mechanisms underlying this sexual dimorphism in the brain. Our results show a major rearrangement of transcriptional patterns, with male and female sharing less than 5% of overlap in genes differentially expressed across brain regions. This small overlap was reproduced in male and female mice after chronic variable stress. Our findings suggest that MDD in males and females arise from the activity of different but also similar gene modules, which share cellular and biological specificity, but which are organized and expressed differently across brain regions in the two sexes. Using viral-mediated gene transfer in the PFC, we showed that the downregulation of the female-specific hub gene DUSP6, a cytoplasmic dual-specificity phosphatase, increases stress susceptibility in females but not in males. We confirmed that this effect associates with increased neuronal excitability in pyramidal neurons. We further showed that these effects take place in a subpopulation of CamKII expressing pyramidal neurons in the PFC. Consistent with the role of DUSP6, these effects were associated with higher phosphorylation levels of ERK in the PFC of females with MDD and stress female mice. Using RNAseq, we showed that DUSP6 downregulation induces its behavioral and molecular effects by modifying the access of ERK to the nucleus thus changing the global organization of transcriptional profiles in the PFC of females.

2-C -122 High-throughput behavioural characterization and precise structure-function analysis of genes and gene variants associated with Autism Spectrum Disorder

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A primary challenge in studying genes associated with Autism Spectrum Disorder (ASD) is the lack of an in vivo system in which to rapidly functionally validate and characterize the large number of candidate risk genes. The sheer number of mutations associated with ASD and the time and money constraints associated with modeling ASD in mammals necessitates an alternative approach. Here, we use the high-throughput capacity of Caenorhabditis elegans as an in vivo platform to functionally validate and characterize ASD-associated genes and their variants. We used our machine vision system, The Multi-Worm Tracker, to characterize morphology, locomotion, and habituation phenotypes of 99 strains of C. elegans covering orthologs of 87 ASD-associated genes. In parallel, we have used CRISPR-Cas9 to generate transgenic C. elegans each expressing a different ASD-associated de novo missense mutation in PTEN in order to validate and assess the functional affects of these putatively pathogenic amino acid substitutions in vivo. This research has generated a large number of novel genotype to phenotype relationships that range from severe developmental delays and uncoordinated movement to subtle deficits in sensory and learning behaviours, as well as detailed structure-function information indicating which ASD-associated PTEN variants are strong function altering mutations. This data will be a powerful in vivo tool to inform future targeted in vivo studies in higher organisms and holds the potential of identifying novel therapeutic targets for ameliorating the effects of ASD.

2-C -123 Functional validation of CACNA1A de novo variants associated with epileptic encephalopathy

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Epileptic encephalopathies (EE) are a genetically heterogeneous group of epilepsies accompanied by cognitive impairments. We recently identified inherited autosomal-dominant loss-of-function (LOF) mutations in CACNA1A gene, encoding the α1 pore-forming unit of the P/Q-type CaV2.1 voltage-gated calcium channel, in patients with EE and a mild form of episodic ataxia. Furthermore, using whole-exome sequencing in a large cohort of children with more severe EE, we identified four different de novo CACNA1A missense variants. CACNA1A missense mutations have traditionally been associated with familial hemiplegic migraine when they cause a gain-of-function (GOF) whereas they result in episodic ataxia (EA2) when they induce a LOF of CaV2.1 channels. However, the functional effects of EE-associated CACNA1A variants are lacking. To investigate whether de novo CACNA1A induce a GOF, LOF or dominant-negative effect on Cav2.1 channel function, we perform whole-cell patch recording in HEK293 cells, co-expressing the wild-type (WT) or mutated (MT) mouse α1A subunit, together with rat β3 and α2δ-1 subunits, and compare whole-cell barium currents (IBa) between WT and MT cells. We successfully generated the WT and 4 MT plasmids, recorded IBa currents from cells transfected with the WT cDNA and validated that a known CACNA1A GOF mutation increases IBa in our own platform. This study will clarify the pathogenicity of de novo variants identified in patients with EE through genomic sequencing and may help guide future therapeutic interventions.

2-C -124 Restoration of hippocampal neural precursor function by ablation of senescent cells in the aged stem cell niche

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Biological aging is characterized by the gradual decline of tissue integrity and function. One putative hallmark for tissue aging is the accumulation of senescent cells - cells which have been permanently arrested due to internal or external stress, such as DNA damage. In the brain, aging is associated with cognitive decline and a decrease in working memory, caused by a reduction in neurogenesis in the

dentate gyrus of the hippocampus. To determine if senescent cells contribute to this decline, we analyzed hippocampal neurogenesis in mice at several time points during normal aging, examining the production of new neurons, precursor/stem cell number and activity, and senescent cell accumulation at each time point. We show that the substantial reductions in hippocampal neurogenesis and precursor number/activity during aging are accompanied by significant increases in the proportion of neural precursor cells (NPCs) that are senescent in the subgranular zone (SGZ) neurogenic niche. Furthermore, we show that pharmacological or genetic reduction of senescent NPCs in vivo rapidly and dramatically increases hippocampal neurogenesis in adult and middle-aged mice. We are currently assessing whether senolytic drugs that restore hippocampal neurogenesis in aged mice also restore hippocampus-associated learning and memory. Taken together, these results indicate that during aging, senescent NPCs accumulate in the hippocampal neurogenic niche and act to inhibit the activity and function of surrounding non-senescent neural stem cells and restrict neurogenesis.

2-C -125 Somatostatin protects blood brain barrier from beta-amyloid induced toxicity

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The human blood-brain barrier (BBB) is an integral part of the neurovascular system and elicit determinant role on the transport of molecules through brain endothelium by restricting permeability. To maintain proper BBB integrity and permeability, tight junction proteins (TJPs) plays a critical role. In Alzheimer's Disease, defective clearance of β-amyloid (Aβ) result in excess accumulation of Aβ that leads to disrupted TJPs organization and increased paracellular permeability in BBB. Somatostatin (SST), a growth hormone inhibitory peptide, functions as a neurotransmitter/neuromodulator in the CNS and also afford neuroprotection in excitotoxicity. Whether this neuroprotective role of SST also involved in protection of BBB is not known. In the present study, using human blood brain endothelial (hCMEC/D3) cells as a model of BBB and Aβ as neurotoxin, we determined the permeability and the organization of TJP in presence or absence of SST. In hCMEC/D3, the expression and organization of TJPs at cell surface was disrupted upon treatment with Aβ, whereas SST ameliorated Aβ induced toxic effect. hCMEC/D3 cells in the presence of Aβ show increased permeability to dextran, however, SST enhanced paracellular permeability restriction in the transwell membrane assay. In addition, SST averted Aβ induced toxicity and restored TJPs organization at the cell surface in dose-dependent manner. SST also enhances the mRNA and protein expression of TJPs in hCMEC/D3 cells. Taken together, these data provide novel insight for the role of SST in protecting BBB integrity in Aβ induced toxicity.

2-C -126 Effect of the cholesteryl ester transfer protein on neural lipid distribution and amyloid-beta generation

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Aims: The cholesteryl ester transfer protein (CETP) is a plasma lipid transfer protein that transports cholesteryl esters from high-density (HDL) to low-density (LDL) and very low-density lipoproteins (VLDL), leading to elevated LDL-C and VLDL-C levels. Epidemiological and genetic studies demonstrated that impaired CETP activity associates with cardiovascular health and lower rate of memory decline. Here, we investigate the role of CETP on the brain-lipid distribution and its effect on Alzheimer's disease progression using cell culture and CETP transgenic mouse models. Methods: Transiently transfected CHO and HEK293T cells as well as a transgenic mouse strain expressing the human CETP under its natural promoter (B6.CBA-Tg(CETP)5203Tall/J) were used in this study. Amyloid-beta peptides were quantified by enzyme-linked immosorbent assay (ELISA). Expression of Alzheimer's disease risk genes

was determined by RT-qPCR and the relative abundance of brain lipids was determined using matrix-assisted laser desorption/ionization-imaging mass spectrometry (MALDI-IMS). Results: CETP activity increased secreted amyloid-beta levels in cell culture models. Expression of hCETP in transgenic animals was induced with a 1% cholesterol diet and led to upregulation of inflammatory cytokines and modulation of Alzheimer's risk genes. Interestingly, hCETP led to altered brain lipid composition and distribution. Conclusion: We conclude that CETP activity may contribute to amyloid-beta generation. Further analyses are required to evaluate its impact on Alzheimer's markers in vivo.

2-C -127 Prolonged high-fat diet worsens acute post-stroke recovery following a small focal ischemic stroke.

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Ischemic stroke is a neurovascular disease with risk factors including the consumption of high fat diet (HFD). Initially, ischemic stroke results in a core of necrotic tissue that cannot be salvaged. Surrounding the core is the penumbra, an area of "at risk" brain tissue that has potential to be rescued. Cells comprising the neurovascular unit (NVU) (neurons, glia cells, microglia and vascular cells) are susceptible to further infarction within the penumbra. Disruption of the NVU can further expand the ischemic core into the penumbra. We examined the effect of prolonged HFD on disruption of the NVU following a small focal ischemic stroke. Male C57BL/6 mice were fed a HFD for 12 weeks prior to stroke. Intracortical injections of the vasoactive peptide Endothelin-1 were used to induce a focal ischemic stroke. Intracardial injection of dextran conjugated Texas Red was used to visualize reperfusion of blood vessels prior to euthanasia. Tissue was collected 7 days post-stroke for analysis. Worse behavioural deficits were observed with HFD that was associated with larger infarct volumes. An increase in neuroinflammation and astrogliosis was seen in HFD fed mice at 7 days post-stroke. A reduction in the survival of neurons within the hypo-perfused area of the infarct was observed in HFD fed mice in comparison to Chow fed mice. HFD led to an increase in infarct volume, neuroinflammation and astrogliosis within the cortex following a focal ischemic stroke that compromised the survival of neurons. Stroke patients that are obese are vulnerable to further infarction of the brain.

2-C -128 GABAergic Innervation of Adult-Generated Neurons in the Post-Stroke Cortex

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Ischemic stroke enhances the proliferation of precursor cells that ectopically migrate to the cortical space surrounding the infarct in the adult brain. The contribution of these new cells to stroke recovery is unknown, as it is unclear whether any of these cells become functionally integrated in the injured cortex. Here, we use a photothrombosis mouse model of focal ischemia and a combination of whole-cell electrophysiology, immunohistochemistry and transgenic reporter strategies to identify and label the dynamic multilineage cellular response within the peri-infarct region of the sensorimotor cortex. We find a population of adult-generated cells that express immature neuronal markers, exhibit voltage-dependent conductances, fire action potentials, and receive GABAergic synaptic input. These findings show that adult-generated, immature neurons have the capacity to integrate into the damaged sensorimotor cortex following stroke, which may permit their functional participation in stroke recovery.

2-C -129 Inhibiting GABA-A receptors to rescue synaptic plasticity after mild traumatic brain injury

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Mild traumatic brain injury (mTBI) is associated with long-term deficits in hippocampus-dependent memory, through mechanisms that are poorly understood. TBI is known to induce a strong inflammatory response in the brain, and inflammation-induced memory impairment has been associated with increased activity of the inhibitory α5 subunit-containing GABA-A receptors (α5GABA-ARs). An increase in the tonic current mediated by α5GABA-ARs is known to impair hippocampal synaptic plasticity. Therefore, we sought to explore whether synaptic plasticity in the hippocampus was reduced in a novel mouse model of mTBI, and if this deficit could be rescued by blocking α5GABA-ARs. Adult male mice were anesthetized, and mTBI was induced using a free weight drop closed-head injury model. One week following mTBI, field post-synaptic potentials (fPSPs) were recorded in the Schaffer collateral-CA1 pathway in hippocampal slices. Long-term potentiation (LTP) was induced using a theta-burst stimulation protocol (TBS) and the slope of the fPSPs was compared before and after TBS in slices from mTBI and sham mice. LTP was reduced in slices from mTBI mice compared with sham-treated mice (122.12 % ± 3.12 % (n=7) vs. 149.25 % ± 3.74 % (n=6); $p < 0.001$, unpaired student's t test). Injection of the α5GABA-AR inverse agonist L-655,708 30 minutes before slicing rescued the deficit in LTP (155.76 % ± 10.72 % (n=3); $p < 0.01$) Thus, the free weight drop closed-head injury model of mTBI induced persistent deficits in synaptic plasticity in the hippocampus, which could be rescued by inhibition of α5GABA-ARs.

2-C -130 Stress induced high frequency/theta cross frequency coupling after post traumatic epilepsy is blocked by CRF receptor antagonism

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Traumatic brain injury (TBI) and its consequences have been a burden on the health care system around the globe. TBI is a major risk factor in the development of pharmacoresistant epilepsy. Considerable evidence suggests that association of stressful life experiences in TBI patients leads to post-traumatic stress disorder and thus may predispose them to epilepsy. However, the mechanism underlying the interaction among TBI, epilepsy, and stress is unclear. High-frequency oscillations (HFO's), a biomarker of epilepsy, can be informative in understanding this interaction. The aim of this project is to understand the role of CRF in inducing excitability in Piriform cortex (PC) after TBI and to investigate the simultaneous neural oscillations occurring in the amygdala during stress in a brain-injured rat, especially possible cross-frequency coupling between theta and high-frequency oscillation bands, with and without a CRFR1 antagonist (CP-154526). We found that PC circuitry is affected in a manner that it easily facilitates the occurrence of epileptic seizures after TBI. And that rats exhibited decreased epileptic behavior during stress when CP-154526 was present. The power of HFOs was found to be coupled to the phase of simultaneous theta oscillations during stress in the TBI-affected rat. Furthermore, this phase-amplitude coupling decoupled in the presence of CP-154526, indicating the role of stress in this response. Our findings provide insight into the mechanism by which individuals affected by TBI develop stress-associated epilepsy.

2-C -131 Role of Swelling-induced Chloride Current in Hypoxic-Ischemic Brain Injury

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Neonatal hypoxic-ischemic brain injury leads to hypoxic-ischemic encephalopathy, which is a major cause of acute mortality and chronic neurological morbidity in neonates. In this study, we investigated the effects of swelling-induced chloride current ICl,swell in hypoxic-ischemic brain injury using 4-(2-Butyl-6,7-dichloro-2-cyclopentylindan-1-on-5-yl) oxybutyric acid (DCPIB), a selective blocker of swelling-induced chloride current ICl,swell. DCPIB was injected intraperitoneally to postnatal seven-day-old (P7) CD1 mouse pups of either sex and a modified hypoxic-ischemic (HI) brain injury model was performed. The outcomes were evaluated using 2,3,5-triphenyl-2H-tetrazolium chloride (TTC) staining, cresyl violet (Nissl) staining and whole brain imaging. Neurobehavioral tests were also used to assess the sensorimotor and vestibular recovery outcomes of the HI. DCPIB attenuates the infarction volume of HI injury in vivo, and improves neurobehavioral performance after HI. Our results indicate that DCPIB has neuroprotective effect on neonatal HI brain injury.

2-C -132 Small molecule stabilization of 14-3-3 protein-protein interactions stimulates axon regeneration

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Damaged central nervous system (CNS) neurons have a poor ability to spontaneously regenerate, causing persistent functional deficits after injury. Therapies that stimulate axon growth are needed to repair CNS damage. 14-3-3 adaptors are hub proteins that are attractive targets to manipulate cell signaling. We identify a positive role for 14-3-3s in axon growth and uncover a developmental regulation of the phosphorylation and function of 14-3-3s. We show that fusicoccin-A (FC-A), a small molecule stabilizer of 14-3-3 protein-protein interactions, stimulates axon growth in vitro and regeneration in vivo. We show that FC-A stabilizes a complex between 14-3-3 and the stress response regulator GCN1, inducing GCN1 turnover and neurite outgrowth. These findings show that 14-3-3 adaptor protein complexes are druggable targets and identify a new class of small molecules that may be further optimized for the repair of CNS damage.

2-C -134 Melatonin and Subjective Measures of Biological Rhythms in Women at Risk for Postpartum Depression: Preliminary Results

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Biological rhythm disturbances occur prior to the onset and as part of mood episodes. In spite of pervasiveness of biological rhythm changes in the perinatal period, these have been little-investigated in postpartum depression, which impacts 7-15% of women. Here we present preliminary results of perinatal biological rhythm profiling using melatonin and subjective reports in 55 women with and without a history of depression or bipolar disorder. Melatonin profiling - the gold standard of measuring circadian phase - was performed using evening salivary sampling, and a morning sample of melatonin's primary metabolite urinary 6-sulphatoxymelatonin. Depressive and anxiety symptoms were measured with the Edinburgh Postnatal Depression (EPDS) and Generalized Anxiety Disorder 7 (GAD7) scales. Subjective biological rhythm disruptions were assessed with the Biological Rhythms Interview in Neuropsychiatry (BRIAN). Women with a history of mood disorders had increased symptoms of depression and anxiety in the 3rd trimester, indicated by higher EPDS and GAD7 scores ($p=0.049$; $p=0.005$). At 6-12 weeks postpartum, group differences in EPDS and GAD7 scores trended towards

significance, as did GAD7 scores at 1-3 weeks postpartum. A linear regression model combining BRIAN scores with group and two melatonin measures accounted for 60.6% variance of EPDS scores and 56.8% variance of GAD7 scores in the 3rd trimester. Our results highlight the association of biological rhythms and postpartum mood and anxiety, setting the precedent for clinical trials of chronotherapies for postpartum mood/anxiety.

2-C -135 Role of MMP-9 in schizophrenia-like behaviors in rodents

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Schizophrenia is recognized by 3 symptoms, classified as positive, negative and cognitive. Positive symptoms may be modelled in experimental animal models by hyperlocomotion, whereas in negative symptoms lack of interest in rewards and problems in social behavior can be demonstrated. Finally, poor working memory may correlate with cognitive symptoms of schizophrenia. Herein, we employed mouse models of schizophrenia for positive, cognitive and negative symptoms and investigated the role of diminished MMP-9 in pathogenesis of schizophrenia in these animals. Mice with genetically lowered MMP-9 levels in heterozygotes (+/-,MMP-9 HET) were employed, along their wild type (WT, +/+) littermates. Since early-life stress is regarded as a factor promoting schizophrenia, we subjected the mice, in some experiments, to daily (for 21 days) encounter with an aggressive conspecific. The results indicate that alterations in the level of active MMP-9 in the brain result in increased sensitivity to locomotor hyperactivity induced by MK-801. On the other hand chronic stress, potentiates negative symptoms of schizophrenia in MMP-9 Het mice such as depressive behaviors and social behaviors impairment. Cognitive symptoms such as poor working memory can be seen in MMP-9 HET control mice. These results support the notion that MMP-9 alterations in brain may play a role in schizophrenia

2-C -136 Generation of a Pten hamartoma tumour syndrome animal model in the CNS, and therapeutic testing

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PTEN Hamartoma Tumour Syndrome (PHTS) is a heterogeneous group of rare, autosomal dominant disorders that are characterized by germline mutations in PTEN. PHTS patients develop hamartomas, which are benign tissue overgrowths comprised of disorganized 'normal' cells. Hamartomas form in all embryological lineages and include CNS lesions that are associated with neurological deficits. A striking feature of PHTS is phenotypic heterogeneity, with hamartomas forming in multiple or only a few tissues. A leading hypothesis to explain this heterogeneity is that second hit mutations create cohorts of mutant cells that act non-cell autonomously to create disorder in neighboring wild-type tissue. Testing this model has been hampered, however, because of the lack of animal models, which have been difficult to generate as most Pten tissue specific conditional knock-outs (cKOs) do not form hamartomas. We report herein the first mouse model that recapitulates hamartoma formation in the CNS. Specifically, we found that a Pten cKO targeted to the peripheral retina reproducibly produces a hamartoma-like lesion in the 'wild-type' central retina. We have recently used this animal model to test the efficacy of sirolimus, an mTor inhibitor that is currently the only known PHTS therapy. Strikingly, treatment with sirolimus significantly worsened morphological defects in Pten cKO retinas, whereas it did not affect wild-type retinal morphology. We have thus generated the first CNS animal model of PHTS, and provide evidence that current therapies may not be successful in targeting CNS malformations.

D – Sensory and Motor Systems

2-D -137 Phantosmia and Phantogeusia Cooccurence

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Introduction: A case with obligate cooccurence of phantosmia and phantogeusia is presented. Methods: Case Study: A 67-year old male, one year prior to presentation, developed an upper respiratory infection inducing smell and taste loss. There was recovery of smell to 10% and savory taste to 30-40% of normal. Odors are either distorted, whereby everything smells chemical-like, or has no smell. Three months after the infection he had the onset of phantosmia which occurs every day for 20 minutes, 5/10 in intensity, which is a chemical odor. At the same time he also noted phantogeusia of the chemical taste of the phantom smell, involving entire mouth, 3-4/10 in intensity. With eating, this taste persists, and the food assumes that taste. The phantosmia and phantogeusia always co-occur and nothing makes them better or worse. Results: Chemosensory Testing: Olfaction: Quick Smell Identification: 2 (hyposmia), Pocket Smell: 1 (anosmia), Alcohol Sniff: 1 (anosmia), Brief Smell Identification: 7 (hyposmia), Retronasal smell index: 1 (abnormal). Gustatory Testing: 6-N-Propylthiouracil Disk Test: 1 (ageusia). Quadrant Taste: weakness to all modalities. MRI: small right parietal and bilateral basal ganglia chronic lacunar infarctions. Discussion: obligate co-occurrence of hallucinations may be due to true primary taste abnormality with retronasal olfaction inducing phantosmia, a primary smell disorder inducing discharge in the retronasal circuits and perceived as phantogeusia, or a single abnormality may exist in tertiary olfactory gustatory orbitofrontal cortex, integration.

2-D -138 Neurogenetics of modulatory cholinergic signaling in C. elegans interneurons

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In the central nervous system, acetylcholine (Ach) acts as a primary neuromodulator. It acts through either nicotinic or muscarinic receptors (mAchRs) to regulate excitatory and inhibitory cortical signalling. These signals contribute to numerous cognitive processes and are critical for sensorimotor control. In the nematode Caenorhabditis elegans, we identified a small circuit that shares similarities with mammalian central cholinergic signalling. It involves a glutamatergic interneuron, RIA, which receives cholinergic feedback from head motor neurons (SMDs) via mAchRs. RIA interneuron muscarinic input is essential for normal head movement. The muscarinic input occurs in phase with head movements during locomotion and regulates gait. The mAChR GAR-3 is essential for this function and mediates local, compartmentalized calcium events in the RIA axon through the mobilization of internal stores. We have identified behavioural and physiological correlates of compromised RIA function and are using them to identify candidate mediators of mAchR function by doing an unbiased reverse genetic screen using feeding RNAi that impact specific neuron classes. Calcium imaging is used to characterize physiological defects in mutant strains in details. Our goal is to identify new components and cellular mechanisms that link muscarinic activation to glutamate release in response to cholinergic modulation.

2-D -139 Where are my whiskers?

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Prior studies reported that the set point of whisking is associated with a slow modulation of neuronal activity in the motor and somatosensory cortices as well as in the. Yet, the functional significance of this central modulation remains unknown. Here we designed a behavioral task that addresses the question of whether rats can voluntarily control the vibrissa set point. Head restrained thirsty rats were rewarded if they maintained their vibrissae protracted within a narrow angular range for up to 2 s. We found that rats can perform this task in the dark without any vibrissa contact. This demonstrates that rats are either aware of the current position of their vibrissae, or that they are aware of the effort required to obtain a reward. As facial muscles that move the vibrissae are devoid of proprioceptors, the question arises as to how rats perform the task. One possibility is that vibrissa position is signaled by receptors that also encode changes in the external environment (i.e., re-afference). Another possibility is that information about vibrissa position derives from a central copy of the motor commands for the intended vibrissa position; this is denoted corollary discharge. We found that rats still perform the task after sensory de-afferentation (transection of the infraorbital nerve). We are currently testing whether lesion of the motor cortex impairs performance. On the basis of the behavioral results, we will assess whether vibrissa position can be decoded from neuronal activity recorded in motor and somatosensory cortices.

2-D -140 Separate Neural Correlates for Spatial and Temporal Gait Control: Evidence from Split-Belt Treadmill Adaptation

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Upon return to tied-belt (TB) treadmill walking after a period of adaptation to a split-belt (SB) treadmill, aftereffects (AE) are present, suggesting with extended exposure, the neural system stores updates to a locomotor plan. This project explored 1) the effects of an auditory dual task on gait adaptation to the SB treadmill; and 2) individual patterns in spatial and temporal gait parameter adaptation with a specific emphasize on "non-responders". Healthy adults (n=49, 23±3years) walked on SB (14 mins; Adaptation) followed by TB walking (De-Adaptation). During Adaptation, participants completed an auditory distraction task requiring verbal responses (0, 8 or 14 mins). Gait changes were not related to a particular distraction group. All participants increased spatial and temporal gait asymmetry with the onset of Adaptation, however distinct adaptation patterns were evident, regardless of distraction group. 57% of participants followed the expected SB adaptation pattern, returning to Baseline TB values by the end of Adaptation and displaying positive AE. 27% of participants only followed the expected adaptation pattern for EITHER spatial OR temporal aspects, and did not show AE in De-Adaptation. Finally, 16% of participants did not adapt spatial nor temporal aspects of gait, indicating a Non-Responder group. Results provide further evidence of distinct neural pathways for control of spatial and temporal aspects of gait. There were healthy young participants unable to adapt to the SB treadmill that is currently unreported in the literature.

2-D -141 Modulation of long-latency afferent inhibition by the sensory afferent volley

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Long-latency afferent inhibition (LAI) is a reflection of sensorimotor integration within the motor cortex. LAI refers to the inhibition of transcranial magnetic stimulation (TMS) motor-evoked potentials (MEPs) caused by the sensory afferent volley evoked by an electrical stimulus delivered to the median or digital nerve. It is unknown how the activation of sensory afferent fibres relates to the magnitude of LAI. Therefore, this study investigated the relationship between LAI and the sensory nerve action potential (SNAP) in two experiments. LAI was obtained by delivering nerve stimulation to either the median or

digital nerve 200 ms prior to a TMS pulse set to elicit either a 1 mV or 0.5 mV response in the first dorsal interosseous (FDI) muscle. Experiment 1 assessed the magnitude of LAI following stimulation of the contralateral median or digital nerve using nerve stimulus intensities of ~25%, 50%, 75%, and 100% of the maximum SNAP. Results show that for both median and digital nerve, LAI increases (i.e. more inhibition) up until 50% of the maximum SNAP. Experiment 2 investigated the magnitude of LAI following stimulation of the ipsilateral median or digital nerve at the four percentages of the maximum SNAP. Results show minimal LAI evoked by ipsilateral nerve stimulation. These results provide both information into the neural mechanisms mediating LAI and practical implications for futures studies using LAI to assess sensorimotor integration.

2-D -142 GENETIC DISSECTION OF THE SPINAL LOCOMOTOR CIRCUIT IN DSCAM MUTANT MICE

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Recently, we have shown that a systemic mutation of DSCAM induces anatomical and neurophysiological changes in the spinal locomotor circuit, thus eventually leading to functional locomotor deficits. In order to genetically identify and characterize the neuronal populations underlying these neurological changes, we conditionally impair DSCAM in glutamatergic neurons by back-crossing VGluT2-cre mice with DSCAMf/f mice. Although adult mutants were able to walk at a higher speed than control mice on a treadmill, they exhibited a more restricted spectrum of locomotor gaits. During fictive locomotion, neonatal mutant spinal cords displayed episodes of synchronization in the neural activity of their left-right ventral roots. Combining retrograde tracing and immunohistochemistry, we found that the number of excitatory back-labeled spinal commissural interneurons was significantly increased in neonatal mutant spinal cords, thus likely contributing to the functional deficits observed in mutants. We are currently assessing the functional contribution of inhibitory neurons. In summary, our studies argue that the expression of DSCAM in excitatory spinal interneurons is important to the normal development of the spinal locomotor circuit.

2-D -143 Action related beta activity in pre-motor cortex during action observation

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Many monkey neurophysiology studies implicate premotor cortex (PM) in action-related decision-making (Cisek & Kalaska 2010). Voluntary movement planning and execution evoke changes in oscillatory activity in the sensorimotor network. Beta synchrony (15-30 Hz) decreases during movement and increases after movement end (Kilavik et al 2013). This modulation may partly reflect motor-decision processes (Tzagarakis et al., 2010). The role of PM might extend beyond motor planning to higher-order cognitive processes. While subjects observe a 3rd party perform a known motor task, the amplitude of post-movement beta rebound in PM may relate to the subjects' recognition of the correctness of observed actions after motor training (Koelewijn et al 2008). However, it is not known whether PM might contribute to the assessment of unfamiliar non-biological visual events prior to motor training. We recorded activity in PM using magnetoencephalography before and after motor training in a two-target pointing task guided by a color-location rule (CLR; Cisek & Kalaska 2004). One subject group learned the CLR by passive observation while the computer performed the task correctly or incorrectly. They then reported their assessment of the observed outcome of further computer-performed trials given the CLR (OBS Task). In a 2nd recording session, they performed the task actively with a joystick (ACT Task). Our results may demonstrate modulation of beta oscillation power in both conditions which implicates PM in cognitive processing of choice-related information.

2-D -144 Spatiotemporal mapping of spontaneous activity in GCaMP6 mice reveals new anatomo-functional boundaries, symmetries and pinwheels of cortical dynamics.

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Connectivity mapping based on resting state activity in mice has revealed functional motifs of correlated activity. However, the rules by which motifs organize into larger functional modules that lead to hemisphere wide spatial-temporal activity sequences is not clear. Transgenic mice expressing GCaMP6s were implanted with a bilateral chronic window covering most the dorsal cortex. Cortical fluorescence was collected in quiet and behaving mice and temporally filtered. Brain activity as well as connectivity was analyzed using seed pixel correlation and clustering approaches. Spectral decomposition of resting state cortical activity revealed the presence of two dominant frequency modes (1Hz and 3Hz), each of them associated with a unique spatial signature of cortical macro-parcellation. Based on assessment of 0.1-1Hz activity we define two macro-organizing principles: the first being a rotating polymodal-association pinwheel structure around which activity flows sequentially between 3 sensory domains; the second principle is correlated activity symmetry planes that exist on many levels within a single domain. In contrast, higher frequency activity yielded 2 larger clusters of co-activated areas. Thus, multiple cortical patterns of activity co-exist in different temporal scales. Beyond the impact of monitoring cortical organization in disease models, this study could open new orientations in developing more advanced brain machine interface technologies (CIHR MOP-12675, FDN-143209)

2-D -145 SPIKE INITIATION PROPERTIES OF MECHANOSENSORY AFFERENTS

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Mechanosensory afferents are a subset of primary afferent neurons that encode tactile input. They are classified into rapidly adapting (RA) and slowly adapting (SA) based on their spike pattern to sustained mechanical stimulation. Whereas RA afferents fire transiently at the stimulus onset and offset, SA afferents fire repetitively throughout. The mechanisms underlying these differences are not clear. Specifically, tactile input is first converted into a receptor potential in the transduction step. The receptor potential is then converted into spikes in the spike initiation step. Here we tested whether spike initiation differs between RA and SA afferents. To characterize spike initiation, both the receptor potential and the spike train must be known. While propagating spikes can be recorded extracellularly or intracellulary from the axon or cell body, the receptor potential must be recorded intracellularly from the axon terminal, which is prohibitively difficult due to the terminal's small caliber. To avoid recording the natural receptor potential, hard-to-measure mechanopotentials were replaced with easy-to-control photopotentials using optogenetics. Using an in vivo technique where extracellular spikes were recorded from the cell bodies of mechanosensory afferents while their terminals were stimulated with light, we show that SA afferents spike repetitively during sustained depolarization whereas RA afferents spike only at the onset of depolarization. These data reveal that spike initiation differs between the peripheral terminals of functionally distinct neuron types.

2-D -146 Plasticity at the synapse between vestibular afferents and central neurons is rapidly offset by the enhancement of local inhibitory pathways: Implications for vestibular prosthetic devices

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Here we examined the neural correlates of behavioral plasticity induced by applying temporally precise stimulation to the vestibular periphery in alert rhesus monkeys. To link changes in neuronal activity with changes in motor performance, we recorded head movements driven by vestibulo-spinal reflexes, as well as the activity of neurons that drive these reflexes during behaviorally relevant stimulation of the vestibular nerve. The probability of evoking a spike from neurons within direct vestibulo-spinal pathways was significantly attenuated on a monosynaptic timescale, in response to vestibular nerve activation. In contrast, the probability of evoking a spike from their afferent input remained constant, suggesting that plasticity (long-term depression (LTD)) was induced at the vestibular afferent-central neuron synapse. The attenuation of this pathway was sufficient to cause a reduction in evoked vestibulo-spinal reflex responses. Interestingly, we found evidence of nearly instantaneous complementary changes in the strength of indirect inhibitory brainstem pathways - with changes in the probability of evoking a spike on a polysynaptic time scale (i.e., 2-3 ms). Taken together, these findings provide evidence that vestibular prosthetic stimulation induces LTD at the first central vestibular synapse. Fortunately, our additional finding that changes at this synapse are rapidly offset by the enhancement of local inhibitory pathways, suggests that complementary brainstem mechanisms are also evoked which in turn function to ensure a relatively robust behavioral performance.

2-D -147 Differential receptive field center-surround organizations give rise to similar levels of neural correlations in three parallel sensory maps in the weakly electric fish Apteronotus leptorhynchus

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[1]McGill University

Understanding the mechanisms by which neural populations encode sensory information remain a central problem in neuroscience. Encoding performance is known to be influenced by the fact that the activities of neurons within a population are not independent but correlated. Such correlations are known to be present almost ubiquitously and greatly complicate our understanding of population codes. Here we investigated how differences in the antagonistic center-surround receptive field (RF) organization influence correlation magnitudes in the activities of electrosensory pyramidal neurons across three parallel sensory maps. Using a computational model, we predict that RF center interactions, known from anatomical studies, will lead to large differences in correlated activity in the different maps. In contrast our data from in vivo electrophysiology reveals that the levels of correlations are nearly identical in all three segments. To explain this surprising result, we additionally incorporated the effects of RF surround to our model, for which no anatomical data exists. By systematically varying both the RF surround gain and size relative to that of the RF center, we explain the similar levels of correlation with the differential RF interactions resultant from the different RF organizations for each of the segments. Our results show further, that RF center overlap alone does not determine correlations but the RF surround contributes as well. This has important implications for understanding how RF interactions lead to the arise of correlated neural activity.

2-D -148 TOLL-LIKE RECEPTOR 4 (TLR4) ACTIVATION IN MEDULLARY DORSAL HORN MEDIATES NOCICEPTIVE RESPONSES IN RAT INFLAMMATORY DENTAL PAIN MODEL

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Application of mustard oil (MO) to the tooth pulp induces central sensitization in the rat medullary dorsal horn (MDH) and sensorimotor nociceptive responses in jaw muscles reflected in increased

electromyographic (EMG) activity. Central sensitization is dependent on activation of MDH microglia. TLR4 is involved in microglial activation in chronic pain conditions but its role in CNS mechanisms of dental pain is unclear. The aim of this study was to evaluate if EMG activities in the anterior digastric (AD) and masseter (MA) muscles induced by MO application into the pulp are dependent on TLR4 processes in MDH. Adult male Sprague-Dawley rats were used (8-13/group). The first maxillary molar pulp was exposed, TLR4 antagonist (LPS-RS, 25 µg/10 µl) or saline (vehicle control) was applied to MDH 10 min before pulpal MO (0.2 µL/95%) application. AD and MA EMG activities were recorded from 15 min prior to LPS-RS or saline application, until 15 min after pulpal MO application. The ipsi- and contralateral MDH regions were removed after euthanasia to quantify TLR4 expression by western blot. There was no significant difference in TLR4 expression between rats receiving MO and naïve control rats. MO induced increased EMG activities in ipsilateral and contralateral AD muscles that were significantly reduced following MDH administration of LPS-RS (2way ANOVA, post-hoc Bonferroni, p=0.0004). TLR4 activation in the MDH may be a mechanism mediating MO-induced dental inflammatory pain in rats.

2-D -149 Modulation of the mouse primary visual cortex neuronal activity by the lateral posterior nucleus

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In mammals, information about the visual world reaches the primary visual cortex (V1) via the lateral geniculate nucleus (LGN), before being processed by higher visual areas. In conjunction with this hierarchical organization, there is a complex network of bidirectional connections between visual cortices and the pulvinar, considered as the largest extrageniculate visual thalamic nucleus. Despite an increasing number of studies on pulvinar, the exact function of this thalamic complex remains unknown. In this study, we investigate the functional impact of the lateral posterior (LP) nucleus (homologue of the primate pulvinar) on the activity of V1 neurons in mice using optogenetic stimulation. Eight wild-type (C57BL/6) mice were injected with a channelrhodopsin-2 gene-carrying viral vector (AAV5.CaMKII.hChR2-eYFP.WPRE) into the LP. Extracellular recordings of the activity of V1 neurons were performed using 16 or 32-channel silicon probes and LP was stimulated with light pulses (470 nm, 20 pulse trains of 5 ms each at 10 Hz) delivered by an optical fiber. Drifting sinewave gratings of varying parameters (direction, contrast, spatial or temporal frequency and size) were used as the visual stimuli. Our data shows that LP stimulation performed in conjunction with visual stimuli decreases neuronal responses by 30 % in average. Furthermore, the response profiles of V1 neurons to size-increasing stimuli were affected. These findings suggest that the LP nucleus can exert a contextual modulation on the activity of neurons in the mouse primary visual cortex. Supp: CIHR.

2-D -150 The computation of unexpected self-motion by the primate cerebellum: evidence for an internal model that accounts for gravity

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

The complex trajectory of head motion poses a particular challenge for the vestibular system because of the presence of the gravity. This is because the sensory periphery does not provide an explicit representation of gravity. Here we asked whether an estimate of gravity is included in the internal model used to compute the difference between self-generated and external self-motion. First, we recorded the responses of cerebellar output neurons (rostral Fastigial nuclei, rFN) during passive self-motion and found that neurons could be divided into three groups: translation, tilt and GIA selective cells. Next, we recorded each cell's responses while monkeys generated voluntary dynamic and static

head tilts. Relative to their response in the passive condition, responses in all cell types in rFN were markedly attenuated (~80%). This implies that the internal model estimate the appropriate reafference (tilt or translation) to generate the cancellation signal. To strengthen this finding, we also recorded neural response during passive translation while the monkeys made simultaneous voluntary head tilt motion. When submitted to concomitant stimuli, both translation and GIA-selective cells' responses provided a precise estimate of the passive motion. We propose a new model that takes into account the complex calculation of gravity to differentiate between self-generated and passively applied head movements. This elegant computation allows to produce accurate vestibulo-driven reflexes. We conclude that sensory function should be studied in context that reproduce natural behaviors.

2-D -151 The impact of primary motor cortex (M1) inactivation on neural activity of the ipsi and contralesional ventral premotor cortex during a reach-to-grasp task

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Following a stroke, the primary motor cortex (M1) is often damaged leading to motor deficits such as a loss of fine motor skills of the contralateral limbs. Imaging studies have shown that there is atypical hemodynamic activity in the remaining intact cortex. However, we have limited understanding of the neuronal reorganization that occurs in this complex and distributed cortical network. In the current series of experiments, chronic multi-electrode array recordings were performed to study the rapid reorganization of neural activity in the ventral premotor cortex (PMv) of both hemispheres after unilateral reversible inactivation of M1. Two macaque monkeys were trained on a pellet retrieval task that required a reach-to-grasp movement with the right or left arm cumulating in a precision grip. In experimental sessions, behavioural and neuronal data were recorded prior and after injection of Muscimol, a potent GABA agonist, in the left M1. The injection induced clear motor deficits with the contralateral right hand. We compared neural activity before and after inactivation by analyzing the within-neuron changes of firing patterns. Whereas the ipsilateral PMv neurons displayed a tonic decrease in activity that was not related to the movement, in the contralateral PMv decreased activity occurred more specifically around the onset of grasp. Our results support that M1 inactivation rapidly induces changes of neural activity during use of the 'paretic' limb that are markedly different in each hemisphere.

2-D -152 Intra and interhemispheric modulation of primary motor cortex outputs by the supplementary motor area in capuchin monkeys (Cebus apella)

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The premotor areas of both hemispheres are highly connected with the primary motor cortex (M1) and contribute to its motor outputs. However, the interactions between premotor areas and M1 are still poorly understood. In particular, no study has yet examined in details the modulation of M1 outputs by the supplementary motor area (SMA) within the same hemisphere (ipsilateral SMA, iSMA) or the opposite hemisphere (contralateral SMA, cSMA) with invasive techniques in non-human primates. In 4 anesthetized capuchin monkeys, we investigated the modulatory effects of iSMA and cSMA on the outputs of M1. A double craniotomy and durectomy exposed iSMA, cSMA and M1. In each area, the hand representation was identified using motor mapping techniques. To evaluate the influence of iSMA and cSMA on the outputs of M1, paired-pulse protocols were conducted while electromyographic (EMG) activity was recorded in hand and forearm muscles. The sampling of multiple cortical sites within iSMA and cSMA allowed us to examine the global profile of interactions of these two areas with M1. Our data

indicate that while iSMA induced slightly more inhibition (54.8%) than facilitation (45.2%), cSMA induced a lot more inhibition (67.3%) than facilitation (32.7%) on the outputs of M1. These intra and interhemispheric modulatory effects differ from those induced by other premotor areas that were investigated in the same monkeys. The unique profile of modulatory effects induced by each premotor area could support the distinct functions they undertake for the production of forelimb movements.

2-D -153 Anatomical characterization of D1 and D2 dopaminergic receptors in the larval zebrafish forebrain

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Neural circuits in the basal ganglia play a central role in determining what actions we perform, however much remains unknown concerning the circuit mechanisms within these structures that underlie behavioral decisions. Remarkably, it has recently been shown that the majority of the components and connections of the mammalian basal ganglia are present in the ancient jawless lamprey, indicating that they are also likely to be present in teleosts. If these circuits exist, the reduction in complexity and unparalleled optical access in larval zebrafish, when compared to the attributes of rodent models of basal ganglia function, should make relationships between basal ganglia activity and behavioral control more salient. To address the function of basal ganglia circuits in zebrafish, we are utilizing Gal4 lines that target the fish's putative direct and indirect pathways which have been shown in mammals to promote or inhibit movement respectively. For the direct pathway, we have already targeted Gal4 to the drd1a locus using CRISPR/Cas9 integration. For the indirect pathway, we are currently developing a drd2a Gal4 line using similar CRISPR/Cas9 genome editing techniques. Stable lines will be anatomical characterized using in situ hybridization and immunohistochemistry methods. Future examination of the function of labeled circuits in these novel transgenic lines using a combination of calcium imaging, optogenetics and behavioural analyses will hopefully provide new insights into conserved circuit mechanisms controlling action selection across species.

2-D -154 Dendritic epidermal T cell control of inflammatory pain

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Inflammatory pain is a result of the body s biological response to inflammation induced by foreign or harmful stimuli such as pathogen (e.g., bacterial) invasion or tissue injury (e.g., post-surgical wound). It has been demonstrated that immune cells enter the site of infection/injury and secrete mediators, which can act on nociceptors to transduce pain signals to the peripheral and central nervous systems. However, the underlying mechanisms surrounding those immune cell(s) mediating the sensitization of nociceptors during inflammation remains unresolved. Dendritic epidermal (γδ) T cells (DETCs) predominate in epidermal tissue near nociceptive sensory nerve fibres, but their contribution to pain remains unknown. Using DETC knockout mice (TCRδ-/-) and wild-type littermate controls (TCRδ+/+), behavioural nociceptive responses were assessed after an intraplantar injection of Complete Freund s Adjuvant, a model of inflammatory pain, and a plantar incisional wound (modelling postoperative pain). Nociceptive activity was characterized using mechanical (von Frey test) and thermal (Hargreaves radiant heat/acetone cold test) assays to assess differences in baseline and acute pain responses. Any differences in nociceptive responses between these two groups may suggest that DETCs and their mediators are driving peripheral sensitization (heightened sensitivity responses) during inflammation. Ultimately, the role that DETCs play in inflammatory pain could provide novel cell-specific drug targets that may provide safe and more effective treatment for this condition.

2-D -155 Chemogenetic inflammatory sensitization of peripheral nociceptors

Hazim Alkhani[1], Ariel Ase[1], Philippe Séguéla[1]
[1]McGill University

Pain is an unpleasant acute or chronic sensation experienced following peripheral injury, inflammation or ischemia. Current models used to investigate pain behaviors in rodents are plagued with pitfalls ranging from lack of spatiotemporal specificity to mandatory invasiveness. Our aim is to generate a spatially specific, non-invasive inflammatory pain model in rodents for the investigation of nociceptive signaling pathways through the utilization of designer receptors exclusively activated by designed drugs (DREADDs). Here, we report a novel transgenic mouse model based on CNO-evoked hM3D (Gq-coupled DREADD)-mediated sensitization of peripheral nociceptive pathways in virally-transduced Nav1.8(+) nociceptors, without administration of any external noxious stimuli or injury. Systemic activation of hM3D induced by intraperitoneal CNO injections evoked strong nocifensive behavior with reduced locomotion, squinting of the eyes and ruffled fur, and intradermal paw injections of CNO resulted in robust acute thermal hyperalgesia and mechanical allodynia as measured in Hargreaves and Von Frey tests. The observed nocifensive behaviors is specifically due to the contribution of small and medium diameter Nav1.8(+) DRG neurons, as indicated by our histology data. Our results provide a proof-of-concept demonstration that chemogenetic interrogation of the contribution of specific classes of genetically-identified primary afferents to neurogenic inflammation is possible, providing a non-invasive, spatially specific pain model that could facilitate drug development and target validation.

2-D -156 Parvalbumin expression in inhibitory neurons of the spinal cord prevents touch inputs from activating nociceptive pathways.

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Neuropathic pain is a chronic debilitating disease that results from nerve damage, persists long after the injury has subsided, and is characterized by spontaneous pain and mechanical hypersensitivity. Loss of inhibitory tone in the dorsal horn of the spinal cord is a major contributor to neuropathic pain. We have previously demonstrated that parvalbumin (PV)-expressing inhibitory interneurons act as gate-keepers that prevent innocuous touch from activating pain-transmitting pathways, and suggested that their activity is decreased after nerve injury. How the output of these neurons decreases after nerve injury is unknown. Cytosolic calcium buffers play an essential role in controlling calcium homeostasis and neuronal activity. We therefore examined whether expression of the calcium buffer PV in these neurons would be affected by nerve injury. Our preliminary data suggest that after nerve injury, PV expression decreases significantly. To examine whether this decrease is related to the mechanical allodynia, we used intra-spinal lentiviral delivery of PV-targeting shRNA in naïve mice, and demonstrate that this decrease, by itself, is sufficient to elicit mechanical allodynia. Subsequent work will examine the intracellular pathways leading to the decreased expression of PV. Understanding how changes in PV expression affect intracellular calcium homeostasis and the output of PV neurons will increase our understanding of the dorsal horn circuitry and may help identify novel therapeutic strategies to alleviate mechanical allodynia in chronic pain disorders.

2-D -157 Characteristics of neural activity in the subthalamic nucleus during unobstructed and visually guided locomotion in the intact, awake cat.

Nabiha Yahiaoui[1], Yannick Mullie[1], Trevor Drew[1]
[1]Université de Montreal

The Basal ganglia (BG) plays an important role in locomotor control. This is emphasized by the impaired walking of patients with neurodegenerative disorders such as Parkinson?s disease (PD) including slow walking with a shuffling gate and small steps, and in more advanced stages, freezing of gait. However, the nature of the BG contribution to the control of locomotion, together with the characteristics of the neural activity during locomotion is poorly understood. In the present study, we examined the properties of the neural activity recorded in the subthalamic nucleus (STN) during unobstructed and visually guided locomotion by recording single neurons in an intact cat trained to step over obstacles attached to a moving treadmill belt. From 52 cells that changed their activity during steps over the obstacle, we concentrate on 37/52 whose activity was related to the contralateral forelimb (coFL). These coFL cells were divided in two groups: (1) neurons (n=17/37) that increased their discharge 2-3 steps before the cat stepped over the obstacle; and (2) neurons (n=20/37) that increased their discharge during the step over the obstacle. Most of the step advanced neurons displayed limb-independent activity while most step related neurons demonstrated limb-selective activity. Most cells (31/37) were also modulated during unobstructed locomotion. These results demonstrate that neurons in the STN contribute to both the planning and execution of gait modifications as well as to the control of unobstructed locomotion.

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2-D -158 The delay of the BOLD fMRI signal does tell you something about neurons

Sébastien Proulx[1], Reza Farivar[1]
[1]McGill

In functional Magnetic Resonance Imaging (fMRI), increased brain activity provokes a delayed response in the Blood Oxygenation Level Dependent (BOLD) signal. The delay arises mostly from the dynamics of the vascular response, but we hypothesize that it contains neurally-relevant information. We predicted that stimulus orientation can be decoded from the pattern of response delays alone. We measured the

delay and amplitude of BOLD responses to orthogonally-oriented visual gratings in 6 healthy subjects. Stimulus orientation was decoded from the pattern of either response delays or amplitudes using a linear Support Vector Machine (SVM) in V1. The pattern of delays alone did allow to decode stimulus orientation (<0.05, binomial distribution). Performances were similar as those obtained with the pattern of amplitudes (>75% correct). Using both delay and amplitude information increased performances to >80% (<0.05 Wilcoxon signed-rank). Analysis of SVM models revealed delay and amplitude orientation-related information to be spatially independent. Finally, with overlay of the two stimuli into a plaid, which is thought to produce more cortical inhibition, responses were delayed by an extra 50ms (<0.05 Wilcoxon signed-rank). Our results show that the fMRI delay does carry neurally-relevant information. This information is different than that carried by signal amplitude and might relate to cortical inhibition. Further work will use independent component analysis to assess whether the delay stems from the summation of excitation and inhibition-related signal components.

2-D -159 Dopaminergic modulation of olfactomotor transformations in lampreys.

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[1]Universite de Montreal, [2]University of Windsor

A neural substrate underlying olfactory-induced locomotion was characterized in lampreys (Derjean et al. 2010; PLoS Biol 8(12): e1000567). It consists of a neural pathway extending from the medial olfactory bulb (OB) to the posterior tuberculum. The olfactory inputs are then relayed to the mesencephalic locomotor region and eventually reach the reticulospinal (RS) cells, which activate the spinal locomotor networks. Modulatory mechanisms acting on this pathway could introduce variability in the behavioural responses of lampreys to olfactory cues. We investigated a possible dopaminergic (DA) modulation of this pathway by using anatomical and physiological techniques. Immunofluorescence experiments showed a DA innervation of the medial region of the OB, but no neurons containing DA were observed in the OB. The DA fibers were found in the same area as projection neurons and primary olfactory afferents. Neurons located in the posterior tuberculum and containing DA were shown to project to the OB by double labelling experiments. Synaptic responses of RS cells to olfactory nerve stimulation were recorded in an in vitro isolated brain preparation. Following local injection of DA in the medial OB, RS cell responses decreased. Furthermore, RS cell responses also decreased after either D1 or D2 receptor agonist injection. However, there was no significant difference in RS cell responses following injections of D1 or D2 receptor antagonist. Altogether, our results show that olfactory inputs to the motor command system are modulated by DA at the level of the OB.

2-D -160 Two-photon calcium imaging defines population encoding of vibrotactile information within excitatory and inhibitory networks of the limb associated mouse somatosensory cortex

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[1]University of Alberta

To distinguish between somatosensory modalities (pressure, vibration, etc.), the somatosensory cortex should process dissimilar stimuli with different patterns of activation. However, a population based study of neuronal tuning to complex somatosensory stimuli has never been reported within the limb associated somatosensory cortex of rodents. Here we used in vivo two-photon Ca2+ imaging to measure somatosensory evoked activity of neuronal networks of up to 250 neurons per optical section. We found that individual neurons within the somatosensory cortex are precisely tuned to particular frequencies of mechanical limb stimulation or broadly tuned to multiple frequencies of fluctuation, thereby forming a population code for sensory processing. These population codes may result from preferential activation of different subsets of cutaneous and musculoskeletal receptors that respond to particular stimuli

features. To examine tuning in parvalbumin-expressing (PV+) inhibitory interneurons and CaMKII-expressing glutamatergic neurons, AAVs were used to express GcAMP6F in CaMKII and PV+ neurons (also co-expressing a red reporter protein). Responses of CaMKII and PV+ neurons were examined during differing paradigms of mechanical or electrical stimulation. We show that PV+ cells are tuned to stimulus intensity, likely as a means to inhibit prolonged activity in excitatory networks. As PV+ cell dysfunction is thought to be a contributor to sensory abnormalities after stroke, ongoing studies are investigating alterations in excitatory and inhibitory networks following cortical stroke.

2-D -161 Motion parallax in electric sensing

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To form spatial representations, animals estimate the relative distance of objects in their environment. Active sensing and the associated motion-based sensory cues play a key role in this process. In active vision, the image of an object moves across a photoreceptor array with a speed that is inversely proportional to the object's distance. This motion-based parallax cue depends on the visual aperture and focal apparatus of the eye. Due to the physics underlying active electric sensing, similar pre-receptor structures are not available to weakly electric fish. Surrounding objects perturb the fish's self-generated electric field and form an electric image on the electro-receptive skin. Despite the fundamental differences between vision and electric sensing, we show that during relative motion, the specific geometry of the electric field gives rise to an electrosensory cue analogous to motion parallax in vision. We hypothesized that weakly electric fish use this cue to estimate distance. To test this, we manipulated the electrosensory parallax cue during a behavioral assay in which fish center between two moving objects and found that fish responded in a manner predicted by our parallax hypothesis. This behavior was reproduced in three species of weakly electric fish from two independent taxa, suggesting that motion parallax is a robust cue for electrosensory distance perception. Supported by grants from MoRitS and the DFG (Deutsche Forschungsgemeinschaft) to JE, and an NSERC Discovery Grant to JEL.

2-D -162 Mutant TDP-43 and pseudophosphorylation of tau protein in cholinergic neurons causes social impairments in rats

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This study investigates the possible interaction of pThr175 tau and mutant TDP-43 in the pathogenesis of the progressive neurodegenerative disease amyotrophic lateral sclerosis (ALS). ChAT-tTA-5/TRE-TDP-43 (M337V) rats were injected bilaterally into the ventral hippocampus with green fluorescent (GFP)-tagged tau constructs. Constructs were GFP vector only, wild-type tau, and Thr175Asp tau (phosphomimic group). Mutant TDP-43 was continually silenced from birth by administrating Doxycycline (Dox) in drinking water, and then expressed by reducing Dox by 50%. Sensory filtering, gait, sociability (time exploring a cage-mate vs empty chamber) and social recognition (time exploring a novel vs familiar rat) was tested prior to Dox withdrawal, post-withdrawal day 14, and post-withdrawal day 28. We found no effect on sensory filtering, but a significant effect of withdrawal on gait and on sociability, where mutant TDP-43 rats showed deteriorating motor abilities and were significantly less social after Dox withdrawal.. At all time points, mutant TDP-43 rats spend more time exploring a novel animal compared to a familiar cage-mate, however, there is a main interaction between injection groups and withdrawal time: the phosphomimic group showed impaired social recognition after dox withdrawal, in

contrast to the other groups. These data provide evidence for a potential interaction of pThr175 tau and mutant TDP-43 in exacerbating ALS symptoms.

2-D -163 Comparing the pattern of interhemispheric interactions of the tentative premotor area in rats to the dorsal and ventral premotor cortex in monkeys

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In primates, in addition to the primary motor cortex (M1), six premotor areas involved in the control of forelimb movements have been identified. In contrast, rats appear to have only two cortical areas involved in forelimb control: a large caudal forelimb area (CFA), corresponding to M1 and a rostral forelimb area (RFA), tentatively corresponding to a premotor area. The goal of our study was to compare the modulatory effects from the RFA on CFA outputs in rats to those from the dorsal or ventral premotor (PMd and PMv respectively) on M1 outputs in cebus monkeys. We used paired pulse stimulation protocols where the electromyographic signal of a suprathreshold test stimulus (Tstim) applied in either CFA (rat), or M1 (monkey) was modulated by a subthreshold conditioning stimulus (Cstim) in either RFA (rat), or PMd, or PMv (monkey) of the contralateral hemisphere (cRFA, cPMd, and cPMv respectively). Applying Cstim in cRFA was more likely to induce facilitatory than inhibitory effects (45.2% vs 10.3%). This patterns was much more similar the one resulting from conditioning cPMd (39.0% vs 24.8%) compared to the one from cPMv (11.0% vs 53.0%). While the proportion of facilitatory effects from RFA and cPMd were comparable ($p=0.119$), cRFA conditioning induced significantly more facilitation than cPMv ($p<0.001$). Conditioning stimulation in cRFA was significantly less likely to induce inhibition than either cPMd or cPMv ($p<0.001$). Our results suggest that while unique, the pattern of interhemispheric interaction from cRFA resembles more the one of cPMd than the one of cPMv.

2-D -164 Catecholaminergic influences on auditory learning in songbirds

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Catecholamines such as norepinephrine (NE) and dopamine (DA) can influence auditory encoding and processing of relatively simple sounds (e.g. tones). However, little is known about their contributions to the processing and learning of more complex sounds. Songbirds such as the zebra finch provide an excellent opportunity to reveal how NE and DA affect the encoding and learning of complex and ethologically-relevant vocalizations since songbirds learn their vocalizations and use them for social communication. We investigated the activity of catecholamine-synthesizing neurons during the developmental learning of song and during adult learning for conspecific song recognition. We observe that NE and DA populations in the locus coeruleus (LC) and ventral tegmental area (VTA), respectively, were significantly more active under tutoring conditions that led to stronger auditory learning. Specifically, social tutoring, which promotes the sensory learning of song, leads to greater immediate early gene expression in NE and DA neurons than passive tutoring. Similarly, NE neurons in the LC are significantly activated when adult male zebra finches were engaged in auditory learning of conspecific songs. Based on behavioral observations, we hypothesize that catecholamines influence auditory learning by modulating attention to songs. Together, these findings highlight a central role of catecholamines in the processing and learning of complex and learned vocalizations and suggest a role of NE and DA neurons in the learning of complex sensory stimuli in other species.

2-D -165 Neural correlates of hindlimb obstacle memory revealed via chronic microelectrode array recordings in parietal area 5 of walking cats

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On complex naturalistic terrain, sensory information about an impending obstacle can modify locomotor movements for avoidance. Furthermore, obstacle information may be stored in memory to modulate future movements if locomotion is delayed. In quadrupeds, such obstacle memory is particularly important for guiding hindleg stepping over an obstacle once it has passed under the body. In cats, deactivation of parietal area 5 via lesions or cortical cooling results in memory deficits in both visually- and tactilely-dependent obstacle memory paradigms. To examine area 5 neuronal contributions to obstacle memory, microelectrode arrays were chronically implanted to record area 5 activity in walking cats. Both visual and tactile obstacle avoidance paradigms, where forward locomotion was delayed following foreleg obstacle clearance, were used to assess obstacle memory. When walking resumed, hindleg stepping was measured as an indicator of whether the animal remembered the obstacle over which the forelegs had stepped. During both visual and tactile paradigms, a population of single units was identified that were selectively active during the delay phase of trials when the obstacle present, but not when the obstacle absent. Furthermore, in a small subset of obstacle present trials, attenuated hindleg step suggested that obstacle was not remembered. In these trials, units that were typically active during the delay were quiescent. Thus such delay-related activity in area 5 may represent a neural correlate of obstacle memory used to modify subsequent hindleg stepping for avoidance.

2-D -166 Eye-head-hand coordination during reaching in head unrestrained Rhesus monkeys.
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To our knowledge, the more natural condition of eye-head-hand coordination during a 3-D reach has not been studied in monkeys. Here we determined how the initial eye and hand position affect the relative timing and accuracy of the eye, hand and head movement when reaching for a target. Eye, head, and hand motion were recorded in two Rhesus monkeys using search coil and touch screen technology, respectively. Animals were seated in a customized 'chair' which allowed the head to move freely and the hand to reach in both depth and direction. Monkeys were trained to touch one of a series of 5 LEDs placed on a horizontal bar at the waist level to control initial hand position. Monkeys were then required to fixate gaze for 400-800 ms on a central target. Finally, this fixation light was extinguished (go signal) and animals were required to reach toward one of 5 targets placed in a horizontal line ahead of their right shoulder with the free movement of their eyes and head. To date, 2000 correct trials from Monkey A have been recorded in this task with 95 % accuracy in reaching movement toward the target. As a control, we recorded 200 correct trials from each monkey toward one of 25 targets (array of 40° horizontal x 20° vertical, visual angle) with initial hand fixation at one location and one initial eye fixation. Currently trials are being recorded in an array of fifteen targets with same dimensions as above. These data will be further quantified for complete spatiotemporal description in behaviors previously tested in humans, with the addition of neurophysiological recordings.

2-D -167 Neural Correlate of Muscle Co-contraction
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Muscle co-contraction is one of the most salient aspects of neuromuscular control and a key element to modulate the stiffness of the limbs and joints. Co-contraction and how it is regulated during motor learning has been well studied by psychophysical experiments involving adaptation to novel physical environments. However, relatively little is known about the neural substrates of co-contraction. We investigated the neural circuits involved in modulating the muscle co-contraction using a force field motor adaptation paradigm and resting-state fMRI approach. Participants interacted with a robotic interface which created novel dynamics. Kinematics and electromyography were recorded during four different stages of motor adaptation followed by a resting-state fMRI scan that monitored brain activity immediately after each stage was completed. A metric of muscle co-contraction was computed from the normalized electromyographic signals. There was a substantial elevation in co-contraction at the earliest stage of the learning that stiffened the arm and provided stability against unpredictable disturbances. As the learning progressed and the central nervous system gradually became able to generate the appropriate joint torques to counteract the disturbance, the co-contraction level declined. We analyzed the change in the strength of functional connectivity in resting-state networks. Our results demonstrate that change in the functional connectivity between posterior cerebellum and primary motor cortex is correlated with a metric of co-contraction.

E - Homeostatic and Neuroendocrine Systems

2-E -168 The pro-inflammatory cytokine Tumour Necrosis Factor alpha excites Subfornical Organ neurons

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Tumor necrosis factor-alpha (TNFα) is a pro-inflammatory cytokine implicated in the neural control of hypertension. It has been shown that TNFα-/- mice do not develop angiotensin II-induced hypertension, although the mechanism for this is unknown. Recent studies suggest that the Subfornical Organ (SFO) is critical for TNFα's hypertensive effects. We therefore used patch-clamp techniques to examine both acute and longer term effects of TNFα on the excitability of dissociated SFO neurons taken from male Sprague-Dawley rats. It was found that bath application of various concentrations (5 fM - 5 nM) of TNFα depolarized 35.5% (n = 22/62) of SFO neurons tested. The proportion of depolarized SFO neurons and the magnitude of depolarizations were concentration-dependent (EC50 = 0.9 pM and EC50 = 0.9 pM, respectively). SFO neurons incubated with TNFα for 24 hours at 575 pM had an elevated firing rate (3.0 ± 0.8 Hz, n = 7) compared to control neurons (0.5 ± 0.2 Hz, n = 7, p = 0.02). Additionally, TNFα incubation reduced the rheobase (5.6 ± 0.5 pA, n = 10) relative to control (11.9 ± 1.7 pA, n =8, p = 0.007). Furthermore, TNFα incubation was found to modulate the transient Na+ current (INa) including the peak INa magnitude (control = 1.7 ± 0.1 nA, n = 15, TNFα = 2.7 ± 0.2 nA, n = 12, $p < 0.001$). Interestingly TNFα incubation had no effect on either the transient potassium current or the delayed rectifier potassium current. These data suggest that TNFα is increasing the acute and long-term excitability in SFO neurons, and this long-term effect is influenced by INa modulation.

2-E -169 Hydrogen sulfide hyperpolarizes Area Postrema neurons to decrease blood pressure in rats

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Hydrogen sulfide (H2S) is an endogenous gasotransmitter with important effects on cardiovascular (CV) function. H2S has classically been found to act at peripheral sites to influence CV control, but has been recently been shown to act at sites in the central nervous system (CNS) to influence blood pressure (BP). Microinjections of H2S into central autonomic control centers such as the paraventricular nucleus and subfornical organ have been shown to increase BP and electrophysiological studies have demonstrated that H2S depolarizes neurons in these areas. The AP is a circumventricular organ with well-documented roles in CV regulation. The present study was undertaken to examine 1) the CV effects of microinjection of NaHS, an H2S donor, into the AP of urethane-anesthetized Sprague Dawley rats and 2) the effects of bath-application of NaHS on excitability of dissociated AP neurons. Microinjection (0.5 µl) of NaHS (5 nM) into the AP caused rapid, short duration (<90 sec) decreases in BP (mean area under the curve (AUC) = -389.2 ± 82.6 mmHg*sec, n=6) and heart rate (mean AUC = -6.6 ± 1.4 beats, n=6). Whole cell perforated patch clamp electrophysiology revealed that bath application of NaHS (1mM) elicited only hyperpolarizing responses (mean Δ in membrane potential = -3.6 ± 0.8 mV) in the majority of AP neurons (n=8/13) tested. These results identify the AP as a CNS site at which H2S may act to lower BP by decreasing the excitability of AP neurons.

2-E -170 Maternal programming of offspring energy mobilization and thyroid hormones

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One of the most important responses to stress is the promotion of energy mobilization mediating the 'fight-or-flight' response. In rodents and other species, predator odor, a predator presence cue, is a mild and ecologically relevant stressor present over evolutionary time that elicit energy mobilization. We ask whether prenatal predator odor exposure could program long-term energy mobilization through changes in thyroid hormones levels as the endocrine mediator facilitating energy availability in an environment predicted to be stressful. To test this hypothesis, we measured the oxygen consumption rate and circulating thyroxine (T4) levels. Unpredictable and inescapable predator odor was presented to a pregnant mouse during the second half of pregnancy while controls were exposed to distilled water. Subsequently, the oxygen consumption rate over 24 hours and in response to predator odor was measured in adult offspring. Offspring from predator odor-exposed dams showed increased energy mobilization during normally lower energetic demanding periods and under a stressful condition. These offspring showed increased T4 levels at baseline and under stress, especially in females. Our findings indicate that prenatal predator odor exposure is sufficient to program the long-term energy mobilization of the offspring, priming the response to stressful situations as shown as the increased oxygen consumption during predator odor exposure. Further investigations are underway to examine the regulation of T4 expression and bioavailability in central and peripheral tissues.

2-E -171 Characterization of dissociated catecholamine-containing GFP-expressing area postrema neurons and their response to GLP-1.

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The area postrema (AP) is brainstem sensory circumventricular organ, well-recognized to play a role in regulating energy balance. Previous work has demonstrated that AP neurons can be categorized by electrophysiological properties, however, the specific properties of catecholaminergic AP neurons are unknown. In order to visually identify catecholaminergic TH neurons of the AP, and quantify their electrical phenotype, we used a transgenic mouse where expression of eGFP is under control of the tyrosine hydroxylase (TH) promoter. Dissociated cultures of AP neurons were prepared and whole cell

voltage clamp was used to examine differences in IA, IK, IH, and INa properties between TH and non-TH AP neurons. While the IA and IK were indistinguishable (n=44,43), 35% of non-TH neurons expressed IH (n=45) while 8% of TH neurons expressed IH (n=46, $p<0.05$). Voltage gated Na+ currents of non-TH neurons also demonstrated significantly more rapid recovery from inactivation than TH neurons (n=13,15; $p<0.05$). While previous studies have suggested that TH-containing AP neurons are the principle responders to GLP-1, the electrical effects of GLP-1 on TH-containing AP neurons have never been investigated. Therefore, we used current clamp recordings to characterize the effects of the GLP-1 agonist Exendin-4 on action potential firing frequency and membrane potential in TH-AP neurons. Our results indicate that TH-AP neurons are an electrophysiologically heterogeneous population and confirm that Exendin-4 depolarizes membrane potential and increases action potential firing frequency.

2-E -172 Sustained Peripheral Inflammation Triggers Central Anandamide Hydrolysis to Promote Anxiety

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There is a high degree of comorbidity between chronic inflammatory conditions and neuropsychiatric disorders; however, the mechanisms underlying these comorbidities are not fully elucidated. The endocannabinoid system reduces anxiety and inflammation, making it an ideal candidate to investigate the mechanisms of these comorbidities. Our aim was to investigate if the endocannabinoid system is altered following peripheral inflammation (colitis), and to determine the relevance of these changes for inflammation-induced anxiety. Colitis was induced by intracolonic administration of trinitrobenzene sulfonic acid to adult male rats. Seven days after induction of colitis, levels of the endocannabinoids, anandamide (AEA) and 2-arachidonylglycerol (2-AG), were measured in the amygdala, hippocampus, hypothalamus and medial prefrontal cortex using mass spectrometry. AEA levels were reduced in the amygdala, hippocampus and medial prefrontal cortex. In the amygdala, the decrease in AEA was accompanied by an increase its metabolic enzyme, fatty acid amide hydrolase (FAAH). In contrast, 2-AG levels were increased in the hippocampus and medial prefrontal cortex. There was also an increase in anxiety levels, as measured by a decreased time spent in the open arm of the elevated plus maze. The colitis-induced increase in anxiety was reversed by an acute intracerebroventricular administration of a FAAH inhibitor (PF-4458945). Our findings reveal a role for AEA in the development of inflammation-induced anxiogenesis and provide a molecular mechanism for the comorbidities of these conditions.

2-E -173 Molecular phenotype of temperature and pressure sensitive neurons in the Organum Vasculosum Lamina Terminalis (OVLT)

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The organum vasculosum lamina terminalis (OVLT) is a circumventricular organ approximately 600 um wide by 700 um high (horizontal plane) that lies anterior to the third ventricle and detects changes in systemic osmolality (Prager-Khoutorsky & Bourque 2015). Preliminary data suggests that thermosensitive neurons in the OVLT synaptically regulate magnocellular neurosecretory cells (MNCs) in the supraoptic nucleus (SON). However, the molecular identity of OVLT neurons, their thermosensitive profile, and their particular location in the OVLT are unknown. Using electrophysiology, single cell RT-PCR, pharmacology, and temperature stimulation protocols, we explored the distribution of neurons containing Trpv1 (TRPV1 WT) or Trpv1dn (□N-TRPV1) within a 500 um wide and 440 um high region of OVLT tissue. Our results show a large distribution of thermosensitive neurons through the OVLT that do

not circumscribe to any particular location. Detailed analysis of these populations shows three temperature responsive behaviors. Single cell RT-PCR results show a well-defined distribution of neurons expressing Trpv1dn across the midline, which is a region that correlates with neurons that are responsive to negative pressure and express the Avpr1a transcript. Alternatively, neurons expressing the Trpv1 transcript are located mostly lateral to the midline core, a region which correlates with neurons that do not respond to negative pressure. Also, we report the finding of an unexpected population of Avpr2 expressing neurons in the lateral regions of the OVLT.

2-E -174 Homeostatic synaptic plasticity in stress circuits

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Corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVN) drive the neuroendocrine response to stress that culminates in an increase in circulating corticosteroids (CORT). This response is typically self-limiting, but pathological conditions, associated with persistent elevations of CORT, suggest escape from negative feedback can occur. Here, we use a model of prolonged CORT exposure to examine the effects on intrinsic and synaptic properties of CRH neurons in the PVN. Mice given access to 25µg/ml CORT in the drinking water for 7 days exhibited a blunted CORT response to swim stress and decreased firing rate of CRH neurons. By contrast, there was a multiplicative increase in mEPSC amplitude, suggesting homeostatic compensation of excitatory synaptic input in response to a decrease in firing. Next, due to the fact that CRH neurons produce BDNF, a neurotrophin released during activity that is implicated in synaptic scaling, we hypothesized that activating BDNF receptors may block the synaptic consequences of the CORT treatment. We included 7,8DHF, a potent TrKB receptor agonist, in the water with CORT. This blocked the increase in synaptic strength. To rule out possible direct effects of CORT on synaptic strength, we injected hM4Di DREADDs into the PVN. Mice were allowed free access to CNO in the drinking water. Following CNO treatment, glutamate synapses showed a similar multiplicative increase in strength. These synaptic changes may contribute to altered hypothalamic-pituitary adrenal axis activity in affective pathologies.

F – Cognition and Behavior

2-F -175 Impact of Vipassana meditation on occipital sleep spindles during a daytime nap and on performance on a procedural memory task

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Introduction: Contemplative practice is known to affect neuroplasticity processes and sleep architecture. Sleep spindles, especially fast (13-16Hz) spindles during NREM sleep have been associated with overnight memory consolidation. This study explores the impact of Vipassana meditation on sleep spindles characteristics during a daytime nap and their relationship with performance to a procedural task between meditators (MED) and non-meditating controls (CTL). Methods: 20 MED (age = 26.3 ± 4.1; f = 10) and 20 CTL (age = 25.0 ± 4.8; f = 10) slept for a daytime nap with a standard polysomnographic montage (frontal, central and occipital derivations). Participants performed on a procedural memory (Wii fit) task before and after the nap. Sleep spindles were detected in NREM2 sleep using an automated in-house algorithm. Results: MED had fewer occipital slow spindles than CTL (M (MED) = 1.75 ± 1.00; M (CTL) = 1.07 ± 0.80; t (38) = 2.385; p = 0.022). Score improvement in MED group was positively

correlated with density of occipital slow spindles (r = .534, p < 0.015) and negatively associated with density of occipital fast spindles (r = - 479; p < 0.032). Discussion: Meditation seems to decrease the number and frequency density of occipital slow spindles. Contrary to our predictions, slow rather than fast spindles were associated with procedural memory learning in MED, suggesting that meditation could promote different sleep-dependent procedural memory consolidation strategies.

2-F -176 Using Eye Movements to Establish a Normative Database of Control Subjects Across the Lifespan

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In order to differentiate neurodevelopmental and neurodegenerative disorders from normal development/aging as early as possible, cognitive decline due to normal development and aging needs to be understood. The oculomotor system is an effective model to probe brain function through analysis of saccadic eye movements. We used a video-based eye tracker capable of measuring saccade performance on an interleaved pro- and anti-saccade task, in subjects aged 5-85 years old. The interleaved task requires subjects to generate anti-saccades (voluntary saccade away from stimulus) or pro-saccades (automatic saccade toward stimulus) depending upon an on-screen colour instruction. This task requires subjects to dynamically update goal-directed objectives on a trial-by-trial basis, amplifying the effects of potential cognitive dysfunction. Subjects younger than 15 and older than 60 years had significantly more direction errors (anti-saccades), increased correct reaction times (anti-saccades), and increased anticipatory saccades (pro- and anti-saccades). Compared to pro-saccades, which were relatively stable across all ages, anti-saccade performance significantly improved during development and declined as a result of aging. Express saccade performance significantly declined due to aging (51 years and older), suggesting that the sensorimotor system is negatively impacted by age. These results provide insight into normal changes that take place across the lifespan in healthy individuals, providing a baseline to evaluate saccade deficits and abnormalities caused by neurological disorders.

2-F -177 Deletion of Atrx in the mouse forebrain results in decreased anxiety and impaired learning and memory

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Emerging evidence indicates that chromatin alterations are required for flexibility of synaptic plasticity during learning and memory. The ATRX intellectual disability gene controls chromatin architecture and gene expression at the epigenetic level and is therefore well suited for the regulation of learning and memory. To understand how ATRX contributes to cognition, we generated mice with conditional inactivation of the Atrx gene in forebrain pyramidal neurons starting at ~P20 using the CaMKII-Cre driver mice. Behaviour testing of Atrx-cKO mice revealed signs of decreased anxiety in both the open field and the elevated plus maze paradigms compared to control mice. Atrx-cKO mice displayed normal short-term memory but defective long-term memory in the Morris water maze and contextual fear conditioning paradigms. Transcriptional profiling was performed on RNA isolated from hippocampi of control and Atrx-cKO mice. The data revealed increased transcript levels of the Tryptophan 2,3-Dioxygenase (Tdo2) gene, that codes for the rate-limiting enzyme in the conversion of tryptophan to kynurenine. Increased TDO2 activity has been linked to decreased serotonin in the mouse brain, as tryptophan is a precursor to this neurotransmitter. Experiments are underway to evaluate TDO2 activity and serotonin levels in the hippocampus of Atrx-cKO mice. Our study identified molecular defects in the hippocampus that could potentially underlie anxiety and memory impairments in Atrx mutant mice.

2-F -178 Investigation of nitric oxide-dependent mechanisms of cocaine-induced place preference and mu opioid receptor expression

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Cocaine administration increases both mu opioid receptor (MOR) expression and nitric oxide (NO) production in brain areas associated with reward. The present study investigated whether the in vivo cocaine-mediated increase in MOR expression is NO-dependent and whether inhibition of this mechanism blocks cocaine reward, as assessed by conditioned place preference (CPP). Male Sprague-Dawley rats were treated with 7-nitroindazole (7-NI) (25mg/kg or 50mg/kg, i.p.), a selective neuronal nitric oxide synthase (nNOS) inhibitor, prior to cocaine administration (20mg/kg, i.p.) during place conditioning (biased design, 4 drug and 4 vehicle pairings). Seventy-two hours following CPP testing, mRNA and protein levels of MOR and nNOS were measured using qPCR and western blotting, respectively. Pre-treatment with either dose of 7-NI did not block cocaine CPP, but did attenuate the increase in MOR mRNA in the nucleus accumbens. However, nNOS mRNA was significantly elevated in the nucleus accumbens of rats pre-treated with 7-NI. These results suggest that NO modulates cocaine-induced MOR expression, but that this mechanism may not play a role in the motivational effects of cocaine. Furthermore, the increase in nNOS mRNA in rats pretreated with 7-NI suggests there is a compensatory response to the inhibition of nNOS activity and NO production.

2-F -179 A systematic review on hyperlexia and its relation to autistic neurocognition

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Four features describe hyperlexia: the presence of a neurodevelopmental disorder, advanced reading skills relative to comprehension skills or general intelligence, the early acquisition of reading skills without explicit teaching, and a strong orientation toward written material. Hyperlexia is considered one of the special abilities often observed in autism, but little information is available on its neurocognitive basis. To further our understanding of the causes and mechanisms involved, we conducted a systematic review on hyperlexia, including 38 case reports with detailed information on 81 individual cases, and 22 group studies including 912 subjects, of which 315 were hyperlexic. We asked: Is the hyperlexic profile associated with autism? Are perceptual strengths often observed in autism involved in the emergence of hyperlexia? Does hyperlexia impact future development? We found that hyperlexia characterises a substantial portion of the autistic spectrum. The prevalence of hyperlexia in autism varies between 6 and 21% in the literature depending on the stringency of the criteria. Furthermore, a majority (84%) of hyperlexic cases were on the autistic spectrum. The perceptual expertise system, specifically the Visual Word Form Area, seems strongly involved in reading in autistics. Hyperlexia could emerge from enhanced perceptual skills. Hyperlexia often precedes the development of language in autism and there is no evidence that it prevents language acquisition or comprehension. We conclude by discussing how hyperlexic skills might be assessed in intervention strategies.

2-F -180 Negative Effects of Noise during Gestation on Spatial Learning and Recognition Memory in Mouse

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Prenatal stress has a diverse variety of negative effects in cognitive performance of both human and nonhuman animals. Few studies, however, have addressed the impact of stress during gestation, particularly noise stress, on mothers' learning and memory. We aimed to investigate the effect of two types of prenatal stresses on the dam's postpartum spatial learning and memory retention. Pregnant mice were randomly assigned to either one of two stress conditions or a control condition. The auditory stress (AS) was a loud intermittent 3000 Hz frequency, whereas the physical stress (PS) consisted of restraint and exposure to an elevated platform from gestational days (GDs) 12-16. Plasma corticosterone (CORT) level was collected on GDs 11 and 17, and Morris water task (MWT) and probe test were carried out one month after parturition. Both stressed groups showed significantly longer time (sec) to reach platform and lower swim speed (m/s) compared with the control group (<0.001). Probe time (sec) was significantly shorter in the AS group than the other groups (0.048). The CORT level (ng/ml) was significantly higher in the post-stress (GD17) than the pre-stress (GD11) assay in both stressed groups (≤0.004), and the ΔCORT level was significantly higher in the stressed groups relative to the control group (0.001). The ΔCORT level showed significant positive correlation with the swim time, as well as significant negative correlation with the probe time in the three groups. The results indicate loud noise exposure during gestation has long-lasting negative effect on mothers' spatial lea

2-F -182 THE EFFECT OF PERIPHERAL NERVE-INJURY ON DEPRESSION AND ANXIETY-LIKE BEHAVIOURS IN MICE

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Introduction/Aim: A large proportion of people suffering from chronic pain also develop comorbid mental health problems. To assess whether rodents can be used as models to study the mechanisms underlying this interaction, we designed a study to determine whether male and female mice develop depressive and anxiety-like behaviours after a peripheral nerve injury. Methods: We assessed mice on a battery of behavioural tests (von frey, tail suspension, and open field tests), then performed either spared-nerve injury or sham surgeries to induce mechanical hypersensitivity in their affected hind paw. After which, mice were re-assessed using the same pre-surgical behavioural tests at either 14, 28, or 42 days post-surgery (not repeated measures design). Mice were run in same-sex groups, where half had a nerve injury and half had a sham surgery (N=6-9). Results: We found that males and females did not show any increased depressive or anxious-like behaviours 14 or 28 days post-nerve injury when compared to sham surgery groups. At 42 days post-surgery, male mice with a nerve injury showed significantly more depressive-like behaviours than sham surgery mice. However, females did not show any differences in depressive-like behaviours between nerve-injury and sham groups. Discussion/Conclusions: These results suggest that findings in male rodents are not necessarily generalizable to females. Additionally, our results suggest that rodent models of neuropathic pain should be assessed over relatively long periods of time due to late-developing behavioural characteristics.

2-F -183 The basal ganglia control the urgency of a reach choice, but not the choice itself

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The basal ganglia (BG) have long been implicated in many aspects of cognition and motor control. To investigate their contribution to decision-making, we recorded cortical and pallidal activity in two monkeys trained to perform a reach selection task that allows us to dissociate the process of deliberation from the moment of commitment and to induce adjustments of their speed-accuracy trade-

off (SAT) in separate blocks of trials. We found that neurons in dorsal premotor (PMd) and primary motor cortex (M1) continuously reflect the evolving sensory evidence guiding the decision. By contrast, BG output via the globus pallidus internus (GPi) remains largely untuned until the commitment time is signaled in PMd/M1. Moreover, the SAT context in which the task was executed strongly modulated a large proportion of GPe and GPi cells. This modulation was congruent with the cells? variation of activity during deliberation within each block: ?build-up? cells tended to be more active during fast than slow blocks, while ?decreasing? cells were less active in fast than slow blocks. Our results suggest that cortical activity reflects a dynamic competition between actions, which is gradually amplified by an urgency signal from the BG that controls the amount of evidence needed before the animal commits to his choice. Eventually, the cortical bias in favor of one of the targets becomes strong enough to engage tuning in the GPi, which constitutes commitment to the action choice. Support: CIHR (MOP-102662), CFI, FRSQ, and EJLB Foundation, FYSSEN and GRSNC fellowships to DT

2-F -184 Cognitive Function in Varsity Football Athletes is Maintained in the Absence of Concussion

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Repetitive sub-clinical head impacts (SHI) are linked to progressive cognitive decline and post mortem CTE diagnoses in pro contact-sport athletes, though there remains little knowledge on the onset of trauma-related cognitive decline in younger athletes. We tested the hypothesis that cognitive function would be impaired as a function of career- and season-long exposure to SHI in collegiate level football athletes. Methods: male football athletes (n=31 age 22.3 ±1.6) completed the Cambridge Brain Sciences (CBS) cognitive battery in the pre- and post-season. Scores were compared in a repeated measures design against an age (20.6 ±1.2) and sex matched control group (n=35). Those with a concussion in the last year were excluded. Pre-season scores were also compared to age- and sex-matched normative values (n>18 000), and transformed into linear composites representing cognitive network function (short-term memory, reasoning, verbal ability). Post-season control tests are ongoing. Results: In the pre-season, there were no significant differences between footballers and controls on any tests, or based on the network composite analysis. Preliminary results suggest that pre-to-post season scores do not differ either between or within groups. Footballers and controls differed from normative values on 6 and 4 tests of cognitive function respectively. Conclusions: Results suggest the maintenance of normal cognitive function, as assessed behaviourally, in the absence of concussion in an elite sport population. Differences between normative and sample means warrant further exploration.

2-F -185 Less is more: high self-controllers rely less on the dorsolateral prefrontal cortex to suppress food craving

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People with high self-control eat less and are more successful at losing weight. Studies implicate the dorsolateral prefrontal cortex (DLPFC) in dietary self-control as suppressing food craving and selecting healthier foods activate the region. They, however capture state self-control (self-control in action) and fail to elucidate the link between trait self-control and eating behaviours. To address this unresolved question, we classified young, healthy people based on the Reward-Based Eating Drive scale as high (0.5 SD below average; n=28) and low self-controllers (0.5 SD above average; n=17). While undergoing fMRI, they performed (1) a food regulation task where they deliberately decreased craving for comfort foods presented in pictures and (2) the Stroop task, in which subjects named the colour of colour words

printed in the corresponding colour or in a different colour. After the scan, they were given a bowl of their favourite chips to eat. The fMRI data was analyzed using SPM8. As expected, high self-controllers compared to the low ate fewer chips and had lower body mass index. The food regulation task and the Stroop task commonly engaged the left DLPFC and bilaterally the fronto-insula cortex and supplementary motor area. Interestingly, food regulation-induced activity in the left DLPFC was significantly smaller in the high versus low self-control group. This study helps further characterize trait dietary self-control by demonstrating that high compared to low self-controllers eat less, have lower body mass index, and rely less on the DLPFC to suppress food craving.

2-F -186 Differential effects of ventral hippocampal CA1 and CA3 inactivation on learned approach-avoidance decision making in rats

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The simultaneous presence of stimuli with opposing valences evokes an approach-avoidance conflict, which can result in the emission of maladaptive responses. The hippocampus is thought to be involved in the resolution of such conflict by exaggerating the value of negative outcomes and increasing the tendency to avoid. Previous work from our laboratory has implicated the ventral, but not dorsal hippocampus in mediating decision making under high approach-avoidance conflict. The present study sought to further investigate the role of different subfields within the ventral hippocampus (vHPC) in learned approach-avoidance conflict. Male Long Evans rats were trained to associate different non-spatial cues with positive, negative and neutral outcomes in three arms of a radial maze. Following successful cue valence acquisition, rats underwent transient inactivation of the CA1 or CA3 subfields of the vHPC using a cocktail of GABAA and GABAB receptor agonists, immediately before a conflict test in which they were presented with a superimposition of positive and negative cues in one arm (conflict cue), and neutral cue in another arm. We found that inactivation of the CA1 subfield led to marked avoidance of the conflict cue, while inactivation of the CA3 subfield resulted in the opposite pattern of behaviour, with significant preference for the conflict cue. Thus, our findings suggest that the CA1 and CA3 region of the vHPC subserve distinct and opposing behaviors in the face of approach-avoidance conflict.

2-F -187 Mesoscale imaging of cortical activity dynamics during REM-like sleep

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Sleep is characterized by loss of consciousness and reduced responsiveness to sensory stimuli. It consists of two primary stages: rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. NREM sleep can be distinguished by slow and high-amplitude "synchronized" cortical activity while REM sleep is characterized by "desynchronized" low-amplitude fast cortical activity. While until recently it has been widely believed that cortical activity during REM sleep is homogeneously desynchronized, using sparse electrophysiological recording a recent study showed that some cortical regions show slow waves during REM sleep. However, the electrophysiological approaches have been unable to resolve the regional structure and dynamics of these activities due to the sparse sampling of electrophysiological technique. Here we used urethane anesthesia as a model of sleep as it induces spontaneous alternation of brain states similar to those observed during natural sleep. Using hippocampal local field potential recordings and mesoscale voltage imaging across most of the mouse cortex, we studied local changes in neuronal activity during REM-like episodes. We found that in the majority of REM-like events, parts of cortex remained synchronized and did not show any transition to the desynchronized state. Our analysis also

revealed that brain activity during REM-like state is made up of complex local patterns that tended to be localized within association cortices.

2-F -188 Subjective value for high calorie snack foods relates to weight gain in the first year students

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Wanting is the psychological process of incentive salience, through which cues predicting reward acquire subjective value. Increased subjective value for food cues can increase the probability of food intake and subsequently lead to weight gain. We tested this hypothesis using the Becker DeGroot Marschak auction paradigm (BDM) to assess the subjective value for high calorie versus low calorie food items in first year university students. 72 first-year students who were living independently for the first time outside of their family's house enrolled in the 8-month long study (mean BMI : 22.6 ± 2.5 SD). Participants underwent fMRI during which they completed the BDM auction task at beginning of the school year. In the BDM task, participants bid on high and low calorie snack foods and trinkets. We measured participants' weight at the beginning and at the end of the school year. The first year students on average gained 3 pounds, but there was a big variability among our participants (mean weight gain : 3.0 ± 6.3 SD). In the brain, the caloric content modulated by subjective value interacted with weight gain. Participants with higher weight gain showed increased BOLD in left vmPFC (MNI: X=-8, Y=38, Z=-10) and left medial OFC (MNI: 3.2, X=-4, Y=48, Z=-10). This result suggests that increased subjective value exhibited in the vmPFC might underlie neurobiological basis of weight gain and obesity.

2-F -189 Acute restraint stress transiently impairs, and subsequently facilitates, performance in Paired Associates Learning assessed in rats using touchscreen-equipped operant conditioning chambers

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Stress affects learning and memory in both humans and rats. The duration of stress has been shown to influence both the valence and intensity of this effect. Generally, chronic stress impairs while acute stress may either impair or facilitate learning and memory. The present study explored the effects of acute stress on a hippocampal dependent paired-associates learning task (PAL) in rats. Male Long Evans rats were trained on PAL using automated touchscreen equipped operant conditioning chambers. Rats were trained to a predefined criterion, approximately 35 days, at which point they were subjected to either 30 minutes of acute restraint stress, or the control condition. PAL performance was assessed immediately following restraint stress and daily for one week following initial stress. Subsequently, animals were subjected to a second session of acute stress and PAL performance assessed immediately afterwards. Initial stress transiently impaired PAL performance on the day of stress, decreasing total trials completed. The second stressor did not significantly effect PAL. During the week following the first stressor, the stressed group performed significantly better

2-F -190 Germ-free mice colonized with GAD microbiota exhibit anxiety-like behaviour and altered BDNF expression, but this change is attenuated with Infliximab treatment

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Accumulating evidence suggests that gut microbiota affects behavior of the host. We investigated whether microbiota from patients with Generalized Anxiety Disorder (GAD) can induce anxiety-like behavior and alter brain chemistry in a murine host. Germ-free NIH Swiss mice (n=27) were colonized with microbiota from a GAD patient (n=13) with severe anxiety or an age and sex-matched healthy control (HC) (n=14). Six mice from each group were treated with infliximab. Three weeks post-colonization, the mice underwent standard psychometric tests. We assessed stool β-defensin and serum kynurenine/tryptophan by ELISA, microbiota profiles by 16S rRNA-based Illumina and BDNF expression via immunofluorescence. Stool β-defensin levels were higher in GAD patients than in HCs. Similarly, β-defensin levels were higher in GAD mice than in HC mice. Microbiota profiles were different in GAD and HC mice and similar to respective human donors. GAD mice exhibited greater anxiety and depressive-like behavior compared to HC mice (open field, digging, marble burying and tail suspension tests). BDNF levels were decreased in the hippocampus and increased in the amygdala of GAD mice. Kynurenine/tryptophan levels were higher in GAD mice. Infliximab-treated mice showed no differences in behavior, central BDNF expression or kynurenine/tryptophan levels. Our results suggest that GAD microbiota has the ability to induce anxiety and depressive-like behavior and alter BDNF expression in a murine host. These changes are accompanied by the activation of the innate immune system and they are TNF-α dependent.

2-F -191 Changes in Women's Performance on the RAVLT Over Time Post-Oophorectomy

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Understanding the role of estrogens in verbal and spatial memory is confounded by age and hormone replacements in older women. However, in women who carry a mutation of the Breast Cancer 1 and 2 genes (BRCA 1/2) a bilateral salpingo-oophorectomy (BSO) is often recommended as prophylaxis for breast and ovarian cancer. This removal of the ovaries abruptly induces an estrogen-deprived state known as surgical menopause. Previous research has shown that estrogen deprivation has a negative impact on cognition, and in later years, this population of women show higher incidence of dementia, including Alzheimer's disease. To better understand the changes over time of ovarian removal on cognition, we evaluated a group of women who have previously undergone BSO (N= 34). In this study, the women received cognitive testing at varying points post-BSO by testing once yearly over a period for 3 years. Through this accelerated longitudinal design, the cognitive performance of oophorectomized women was captured ranging from .5 to 12 years post-BSO. One measure, the Rey Auditory Verbal Learning Test (RAVLT), evaluates short-term auditory-verbal memory, encoding processes, rate of learning, and retention of information. Preliminary results from the RAVLT show that women with BSO have a significant decline in performance with regards to time since-BSO. This provides useful evidence towards evaluating the link between early deficits post-BSO and the eventual increase in dementia in later years, and suggests that early decline in verbal memory may be attributed to impaired hippocampal function.

2-F -192 The role of the hippocampus in goal-directed navigation

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The aim was to explore the idea that the prospective firing of hippocampal place cells observed during awake sharp wave-ripple (SWR) events is causally implicated in planning of future routes to remembered goal locations. Using a reward searching task with 'home' and 'random' locations, combined with simultaneous recording of large numbers of place cells, Pfeiffer and Foster (Nature, 2013) discovered that hippocampal place cell sequences represent future trajectories to remembered goals. We therefore investigated whether hippocampal cell-firing is necessary for this type of goal-directed navigation. Rats were trained in an open field with a 7×7 grid of possible reward locations. Each day, a different location was designated as 'home' and rats learned to navigate between it and successive 'random' reward locations. Local infusion of the γ-aminobutyric acid-A (GABA-A) receptor agonist muscimol was used to inactivate the hippocampus. The muscimol dose was calibrated to block (1) evoked hippocampal activity and (2) place memory in the watermaze. Muscimol-induced hippocampal inactivation did impair the rate of learning of the new daily 'home' location, but had minimal effect on differential navigation during later trials. Electrophysiological studies of place cells in freely moving rats offer valuable insights into the physiology of goal-directed navigation, but they typically constitute only correlational evidence. Surprisingly, we now observe that hippocampal cell-firing is not necessary for execution of the Pfeiffer and Foster task (2013). Supported by GRIDMAP (ICT-FET, FP7)

2-F -193 Estimating the frequency of Automated Symbolic Orienting using a trial-by-trial analysis

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It has now been repeatedly demonstrated that humans spontaneously orient their attention in response to common symbols like arrows, engaging the so-called Automated Symbolic Orienting (ASO). Here we assessed whether these results reflected consistent attentional orienting in most available instances (i.e., trials) or an effect of averaging the large attentional benefits occurring on a handful of trials. To do so, we collected data from 25 participants who performed a standard cuing procedure in which left and right pointing arrows as well as neutral inward arrows served as attentional cues. Participants detected peripheral targets, which occurred equally often at a left and right location. Data were analyzed in two ways. First, a standard group-based ANOVA replicated a wealth of past research showing overall reliable ASO effects for cued (i.e., those indicated by arrow cues) relative to uncued targets (i.e., those not indicated by arrow cues). Second, to address our main question, we calculated the proportion of cued and uncued trials that were significantly faster than the neutral. A greater proportion of cued trials (20%) were facilitated as compared to uncued trials (16%). Together these results suggest that ASO reflects neither the consistent orienting throughout nor the effect of averaging over datasets containing a few extreme trials.

2-F -194 Modulation of Arc expression in the olfactory bulb by social preference

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It has long been known that rodents can impart preference for scents and flavors of food through social contact. While a great deal of behavioral work has been done on the social transmission of food preference (STFP), relatively few experiments have investigated the neurobiological substrate that support STFP. Towards this goal, we investigate whether the development of STFP alters olfactory bulb activity. Studies have shown that another form of socially transmitted preferences, the pairing an odour with tactile stimulation, alters the olfactory bulb response to the preferred odor. More specifically, the

preferred odour is represented by a larger ensemble of mitral cells, more reliably recruited upon exposure to the preferred odour. To test whether a similar process occurs in the adult following STFP, we expose adult male Sprague Dawley rats to two flavors (cocoa and cinnamon) and impart a preference for one of the flavors (counterbalanced) using a standard STFP protocol. The following day, groups of rats (n = 6/group) are exposed to either the preferred odor twice (P/P), the non-preferred odor twice (NP/NP), or both odors (P/NP), with each exposure space 30 min apart. The size and pattern of the ensemble activated by each odor can then be determined by examining the compartmental expression of Arc. If, as hypothesized, STFP causes the preferred odor to induce a larger and more specific pattern of mitral cell activity, this suggests that the large body of data on the mechanisms of preference development through tactile stimulation may also apply to the STFP paradigm

2-F -195 Blockade of T-type calcium channels reduces conditioned fear in an animal model of absence epilepsy

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Genetic Absence Epilepsy Rats from Strasbourg (GAERS) are a rodent model of childhood absence epilepsy that display a gain-of-function missense mutation in the gene encoding the Cav3.2 T-type calcium channel. GAERS have previously been demonstrated to have heightened learning and delayed extinction of Pavlovian fear conditioning. Our objective was to examine the effects of the pan-T-type calcium channel blocker, Z944, on conditioned fear behaviour in GAERS, the Non-Epileptic Control (NEC) strain, and Wistars. Z944 (5mg/kg Wistars only, 10mg/kg in all strains; ip) was administered prior to either the conditioning or recall of delay-conditioned fear. Extinction of conditioned fear was also examined. Z944 treatment prior to conditioning enhanced freezing during conditioning, but reduced freezing during recall in all strains. In GAERS, Z944 treatment prior to conditioning reduced freezing during extinction. Z944 treatment prior to recall increased freezing during initial exposure to context cues during recall in all strains. Overall, Z944 treatment prior to conditioning normalized fear behaviour in GAERS whereas treatment in NEC and Wistar animals impaired recall of conditioned fear. These results demonstrate that T-type calcium channels contribute to the neural systems that mediate the learning and memory of conditioned fear. Continued research into the therapeutic potential of T-type calcium channel regulation may be particularly fruitful for the treatment of disorders characterized by enhanced memory of negative experiences.

2-F -196 Proprioception calibrates object size constancy for grasping but not perception in limited viewing conditions

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Observers typically perceive an object as being the same size even when it is viewed at different distances. People also use the same grip aperture when grasping an object positioned at different viewing distances in peripersonal space. Perceptual size constancy has been shown to depend on a range of distance cues, each of which will be weighted differently in different viewing conditions. It is still unclear whether or not the same distance cues (and the same cue weighting) are used to calibrate size constancy for grasping. To address this question, participants were asked either to grasp or to manually estimate (using their right hand) the size of spheres presented at different distances in a full-viewing condition (light on, binocular viewing) or in a limited-viewing condition (light off, monocular viewing through a 1 mm hole). In the full-viewing condition, participants showed size constancy in both tasks. In the limited-viewing condition, participants no longer showed size constancy, opening their hand

wider when the object was closer in both tasks. We then asked participants to perform the same tasks while their left hand was holding a pedestal under the sphere. Remarkably, the proprioceptive cues from holding the pedestal with their left hand dramatically restored size constancy in the grasping task but not in the manual estimation task. These results suggest that proprioceptive information can support size constancy in grasping when visual distance cues are severely limited, but such cues are not sufficient to support size constancy in perception.

2-F -197 Target presence affects the eye movement kinematics and behaviour of non-human primates in virtual navigation tasks

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As technology and scientific knowledge have advanced, the possibility and necessity of using virtual environments to run experiments has arrived, and the eye movements that are used to explore the environments need to be characterized. We trained two rhesus macaques to use a joystick to navigate in a virtual environment (VE) during a complex learning task and a foraging task. We analyzed gaze on screen behaviour and eye movement behaviours: saccades, fixations, and smooth pursuits. We also analysed the kinematics of saccades across the tasks and within periods of the Learning task. We found that gaze on screen as a function of the proportion of a trial changed based on whether there was a target currently in the environment. There was a median trial proportion of 47% when the subject was just navigating. When there were rewarded targets, the median gaze-on-screen was 80% and 91% for the Foraging and Learning tasks. For saccade kinematics, we calculated the main sequence by matching saccades on start location (<5dva) and direction (<10°) in bins of 3dva amplitude. We ran repeated measures ANOVAs to test for differences and fit a non-linear model to estimate the change in the main sequence. We did not find an effect of static vs dynamic phase of stimuli in the VE. We did find that saccades were 7% faster when there were rewarded objects on the screen in VEs, and that the different levels of difficulty in our task did not alter the main sequence. There is likely an arousal/engagement change between simple virtual navigation and navigation towards a rewarded target.

2-F -198 Effects of exposure to an ecologically relevant toxicant mixture during pregnancy on hippocampal volumes in post-partum rat dam brains

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Complex combinations of environmental toxicants are highly prevalent in Northern Canada, placing a higher toxicant body burden on the Northern population. Twenty-seven common chemicals including polychlorinated biphenyls, organochlorine pesticides, and methylmercury, were used as part of an ecologically relevant toxicant mixture. The results of earlier research show the damaging effects of this mixture on fetal development; however little research has explored its impact on maternal physiology or behaviour. The hippocampus plays an important role in the spatial learning and memory processes related to maternal behaviour, and due to its high plasticity, may be particularly vulnerable to such environmental insults. The objective of this study was to assess the impact of exposure to the contaminant mixture during pregnancy on maternal CA1, CA3, and dentate gyrus (DG) hippocampal volumes. Pregnant Sprague-Dawley rats were dosed daily with 4.0 mg/kg of the mixture or equal volume of vehicle from gestational day 1 to postnatal day 20. Brains were collected on postpartum day 21. Left and right CA1, CA3, and DG volumes were calculated; ANOVAs were used to assess any treatment effects. Preliminary results suggest that exposure to the contaminant mixture did not significantly alter the CA1 volume. Final calculations are underway for the CA3 and DG. Any effects of this contaminant

mixture on the maternal brain may have functional consequences with respect to the quality of maternal care that is provided to the offspring, and as such may impact offspring neurodevelopment.

2-F -199 The effect of Neuroligin 2 absence on sleep architecture and EEG activity in mice

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Sleep disorders are co-morbid with most psychiatric disorders, but the link between these is not well understood. Neuroligin-2 (NLGN2) is a cell adhesion molecule that plays roles in synapse formation and neurotransmission. Moreover, NLGN2 has been associated with schizophrenia, but its implication in sleep remains unexplored. We investigated the effect of Nlgn2 knockout (KO) on sleep architecture and EEG activity in mice. Two electroencephalography (EEG) electrodes were implanted above the right hemisphere in Nlgn2 KO mice and littermates to record EEG for 24h. Vigilance states (wakefulness, rapid eye movement sleep [REM], non-REM sleep [NR]) were identified on 4sec epochs and vigilance state duration was calculated. Spectral analysis was performed on epochs without artifact using to Fast Fourier Transform. Nlgn2 KO mice showed more wakefulness as well as a less NR and REM compared to wild-type mice. The changes in wakefulness and sleep durations originated from alterations during the 12h dark period because KO mice exhibited normal sleep/wakefulness duration during the 12h light period. The relative spectra showed a significant genotype effect for fast frequencies (25-50Hz) during all vigilance states, with KO mice having less activity than littermates. A shift in dominant peak frequency during REM and wakefulness was also observed. These data suggest that NLGN2 participates in the regulation of sleep duration as well as EEG activity during wakefulness and sleep.

2-F -200 INCREASED INCENTIVE MOTIVATION FOR COCAINE IS LINKED TO HEIGHTENED COCAINE-INDUCED GENE REGULATION IN FRONTOSTRIATAL BRAIN REGIONS

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A challenge in addiction research is distinguishing between neuroplasticity linked to addiction from that resulting from mere drug exposure. We have been studying how cocaine access conditions impact the development of addiction-like behaviours in rats, in hopes of uncovering brain changes involved in the addiction process. Frontostriatal circuits (FS) are recruited after long-term cocaine use. If FS are involved in addiction, they should be preferentially activated in rats that show addiction-like symptoms. We studied cocaine-induced gene regulation in FS following intermittent access (IntA) to rapid cocaine infusions vs. continuous access (ContA) to slow ones. IntA produces the repeated spikes in brain drug levels thought to model cocaine use by addicts and increases incentive motivation for the drug (Zimmer & al. 2012; Beveridge & al. 2012). ContA to slower injections supports high levels of intake, without promoting addiction-like behaviours (Minogianis & al. 2013; Wakabayashi & al. 2010). Rats had IntA to rapid iv cocaine infusions (5s; 0.25 mg/kg/inf) or ContA to slow infusions (90s) 6h/d for 9 sessions. Motivation for cocaine was assessed under progressive ratio. Following a final test session, brains were extracted and processed for in situ hybridization of c-fos mRNA. IntA rats took less cocaine than ContA rats, but showed greater motivation for the drug and expressed more c-fos mRNA in the orbitofrontal and prelimbic cortices, and the dorsal striatum. Thus, the increased motivation to take drug seen in addiction may involve greater drug-induced engagement of FS.

2-F -201 Identification of an inhibitory hippocampal-thalamic pathway that mediates remote memory retrieval

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Analysis of a fear memory functional network (Wheeler, 2013) revealed that remote memory recall involves an increase in functional connectivity between thalamic, hippocampal and neocortical brain regions. Further analysis of this remote memory network revealed a unique pattern of negative functional connections between the anterodorsal thalamic nucleus (ADn) and the rest of the network. This led us to hypothesize that inhibition of the ADn may occur during remote memory retrieval. We virally infused an adeno-associated virus (AAV) carrying the excitatory opsin ChR2 in the ADn and trained the mice in a fear conditioning. When we optogenetically excited ADn neurons during remote memory recall we found that ADn activation impaired conditioned freezing. Next, we examined the anatomical connectivity, and found that in addition to functional connections, ADn is also structurally connected with hippocampal and neocortical regions that are highly implicated in memory consolidation. In particular, we identified strong inhibitory projections from the CA3 to the ADn that could potentially mediate the inhibition of ADn. To test this, we bilaterally infused a cre-recombinase dependent AAV carrying the inhibitory opsin eArch in the CA3 of VGATcre mice to specifically inhibit GABAergic projections from the CA3 to the ADn. When we inhibited these projections during the remote memory test, mice showed impaired memory performances. Here, we show for the first time, that remote memory recall engages and requires a unique negative functional and structural connection from the CA3 to the ADn.

2-F -202 FXR1P limits long-term memory, perseverative behavior and L-LTP by regulating GluA2.

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Proper cognitive function requires specific molecular and cellular mechanisms that allow for proper gene expression and circuitry physiology. Control of protein synthesis by mRNA binding proteins represents a major mechanism for regulating protein abundance and site-specific localization of proteins that underlie synaptic plasticity and cognitive function. We discovered that a member of the Fragile X family of proteins, Fragile-X related protein (FXR1P), associates with protein synthesis machinery in neuronal dendrites and plays an important role in limiting late-phase long-term potentiation (L-LTP) and long-term memory recall. Specifically, conditional deletion of FXR1P from the postnatal forebrain enhanced hippocampal L-LTP and improved spatial memory recall (Cook, Nuro et al., Cell Reports 2014). Furthermore, loss of FXR1P increased translation of the mRNA encoding the AMPA receptor subunit GluA2 as well as the amount of GluA2 subunits that are selectively mobilized to synapses upon long-lasting synaptic plasticity. In line with these results, we found that FXR1P deletion increases long-term memory storage and induces perseverative behavior in the Barnes Maze test. In conclusion, our study has identified a new mechanism involving FXR1P for regulating long-lasting synaptic plasticity and spatial memory storage. We are currently following up on these results to further dissect the molecular mechanisms involved. Future studies will also determine if and how FXR1P may be related to CNS disorders associated with cognitive and intellectual disability.

2-F -203 Comparing the Neural Correlates of Mental Flexibility in Children with Neurodevelopmental Disorders: an MEG Investigation

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Neurodevelopmental disorders (NDs), including autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), are characterized by impaired development of central nervous system function. This impacts executive functions, including mental flexibility (MF), the ability to alter mental processes in adaptation to environmental changes. Due to the heterogeneity of NDs, we hypothesized that the neurobiological substrates underlying MF would differ across ND subtypes. To investigate, we recruited 90 children with NDs (8-15yrs; 20F; 38ASD, 30ADHD, 22OCD) to complete an MF task while undergoing a magnetoencephalography (MEG) scan. The MF task required matching of stimuli, with matching criteria shifting every few trials. Groups performed comparably. MEG data were source reconstructed to create high resolution spatiotemporal activity maps of brain regions significantly involved in the task. MEG revealed similar patterns of activation for ASD and ADHD, with sustained early parietal activity and late recruitment of frontal regions. OCD displayed the expected activations in frontal regions, however their parietal activity was sustained also. This trend of greater similarities between ASD and ADHD, compared to OCD, is consistent with suggestions that the former two are more similar in etiology. Our results suggest that while the various groups of NDs show some differences in MF processing, they also share common neurobiological substrates. This is the first functional neuroimaging study to investigate MF across multiple NDs.

2-F -204 Muscarinic M1 receptor modulation of prefrontal cortical activity in monkeys during antisaccade performance

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The dorsolateral prefrontal cortex (DLPFC) plays a crucial role in cognitive control and the inhibition of inappropriate responses. Ascending cholinergic innervation of DLPFC has important contributions to the physiology and effective functioning of prefrontal circuitry. We, and other groups have previously shown that the muscarinic antagonist, scopolamine, has a disruptive influence on prefrontal activity related to working memory maintenance. Here, we examined muscarinic receptor subtypes to further delineate the specificity of the inhibitory effects of scopolamine. Based upon anatomical expression and prior physiological data, we hypothesized that muscarinic M1 receptor stimulation would increase prefrontal excitability. Here we applied selective M1 allosteric and orthosteric modulators using microiontophoresis and other methods to examine the local effects of M1 receptor modulation on prefrontal neurophysiology in monkey DLPFC, while the subjects were engaged in performance of a rule-guided pro- and antisaccade task. We found that, contrary to our hypothesis, M1 receptor stimulation was predominantly inhibitory in monkey DLPFC. Furthermore, M1 receptor blockade, unlike scopolamine application, did not uniformly result in suppression of neuronal excitability. These results suggest that the suppressive effects of muscarinic blockade with scopolamine may be mediated by more complex signaling mechanisms and/or involving other muscarinic receptor subtypes. Our findings have interesting implications for the study of cholinergic neuropharmacology of the prefrontal cortex.

2-F -205 Extra-hippocampal contributions to associative memory retrieval

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Memory research has established that memory processes rely on the medial temporal lobe (MTL). This has led to an intense research focus on the MTL, but may have resulted in failure to detect critical contributions of other brain regions to memory processes. Thalamic subregions, for example, may play an important role in retrieval of memory associations (Pergola et al., 2013), but for the most part, this research topic has received little attention in the literature. The current study uses an associative memory paradigm and 3 tesla whole brain multiband functional magnetic resonance imaging (fMRI) to test involvement of MTL and extra-MTL structures in associative memory. A paradigm by Hannula and Ranganath (2009) was used, providing the opportunity to both replicate and extend previous findings. During the encoding phase, scenes are presented with faces. The memory test phase then starts with a studied scene (i.e. a memory cue) and prompts the participant to retrieve and envision the previously paired face during a 7 second delay. Finally the participant makes a memory decision by choosing between 3 studied faces the one that was associated with the current scene. During the delay phase, significant activations were observed ($p<0.05$ FDR corrected) within the thalamus, dorsal striatum and ventral visual processing stream, which may enable the successful retrieval of the associated face. Future analyses will explore how these activations contribute to task performance. The current work shows initial evidence for contributions of extra-MTL structures in associative memory.

2-F -206 Representational similarity analysis reveals similarity between subjects in movie viewing using MEG

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Reliable brain activity synchronization among participants induced by naturalistic stimuli such as movies has recently been increasingly reported. Hemodynamic inter-subject correlations (ISC) studies indicated that neuronal population prototypical pattern exists (Hasson, Nir et al. 2004). Controversial remains on which frequency response of the neural population contributes to prototypical pattern. On one hand, low frequency brain oscillations showed significant inter-subject correlation rather than high frequency bands in many previous reports (Lankinen, Saari et al. 2014, Chang, Jaaskelainen et al. 2015); on the other hand, high frequency brain bands such as gamma band were involved in visual processing. These findings suggests that there exist distinct prototypical patterns for low frequency band and high frequency band. New method analysing different roles for low frequency bands and high frequency bands needs to be established for describing prototypical spectral brain pattern. In our study, we found that low frequency oscillation bands contributed to the prototypical time pattern by showing higher time-course ISC, while high frequency bands could not. High frequency bands contributed to the prototypical pattern in a distinct way, which is representational similarity of the different movie scenes. We proved the distinct pattern of different frequency bands, and established a solid way to investigate the prototypical pattern during naturalistic viewing in high frequency bands.

2-F -207 Effects of catecholamines on motivation in macaque monkeys

Mavis Kusi[1], Lindsey Thurston[1], Catherine Crandell[1], Martin Paré[1]
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We tested whether catecholamines have a direct influence on cognition or an indirect effect by enhancing motivation (task engagement) by examining the effects of the catecholamine reuptake inhibitor atomoxetine (ATX) on working memory and motivation in three rhesus monkeys. The monkeys performed a change detection task probing working memory capacity. We found that none of the doses tested (0.03 - 3.0 mg/kg) had a significant effect on response accuracy and response latency. However, ATX had a moderate effect on enhancing some measures of task engagement: the proportion of trials

that were not completed (i.e., aborted), the proportion of trials the animals failed to initiate, and the total number of trials. To more directly assess the effects of ATX on motivation, we tested the monkeys on a task with a progressive-ratio schedule of reinforcement, similar to tasks used to evaluate the reinforcing effects of drugs of abuse. In this task, the animal must fixate a gradually increasing number of visual stimuli to obtain one reinforcer. After each successful trial, the number of fixation stimuli required is increased by step of one until the animal stops responding or consistently fails to complete the current level (i.e., the breakpoint). ATX was observed to raise the breakpoint; this effect depended on the dose. These results suggest that, similarly to the catecholamine reuptake inhibitor methylphenidate (Oemisch et al., Neuropharmacology, 2016), ATX does not directly enhance cognitive skills such as working memory. These drugs may be best described as boosting motivation.

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2-F -208 Cognitive and non-cognitive phenotypes in the 5xFAD mouse model of Alzheimer's Disease

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[1]Robarts Research Institute, University of Western Ontario, [2]Robarts Research Institute, [3]University of Guelph

Alzheimer's Disease (AD) is a disabling chronic disorder characterized by progressive cognitive impairment, often beginning with memory loss and executive abnormalities. Patients may also experience gait disturbances. Given the high prevalence and poor prognosis of AD, the characterization of animal models with face validity reproducing cognitive and non-cognitive disturbances is extremely important. In this study, we performed a longitudinal evaluation of visual discrimination and cognitive flexibility in the 5xFAD mouse model of AD using the Bussey-Saksida pairwise visual discrimination (PVD) touchscreen task at 4, 7 and 10 months of age. Following the completion of the last time-point, the mice were tested for various non-cognitive measures, including locomotor activity, gait and grip strength. Lastly, amyloid pathology was confirmed in these mice and because they were food restricted to perform touchscreen tests, the effect of mild-food restriction on this pathology was also investigated.

Food restriction did not affect amyloid pathology and at all time-points 5xFAD mice had no deficits in visual discrimination. However, at 10 months of age 5xFAD mice take longer than controls to respond to the task and collect their reward. 5xFAD mice also demonstrate gait disturbances. In summary, we provide a comprehensive evaluation of phenotypes in the 5xFAD mouse line that could be used for testing potential AD treatments.

2-F -209 Explicit Timing Accuracy Correlates with Cognitive Status of Older Adults

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[1]University of Manitoba

The early effects of age-related cognitive decline on explicit timing have been widely reported. However, it is not clear to what extent the measures of internal clock and working memory are predictive of cognitive function in older adults. In this study, we examined three target intervals (i.e., 2, 6, 10 s) under Production and Reproduction tasks to assess the performances of internal clock and working memory, respectively. Participants were 36 older adults (19 females) with age of 68.4±5.1 yr and Montreal Cognitive Assessment (MoCA) scores of 27.9±2.0. In the Reproduction task, the participants were asked to reproduce the duration of a previously-seen stimulus generated by a virtual reality program, while in the Production task the participants had to produce a target interval explicitly requested by the program. Each task consisted of nine trials with three repetitions of each target interval in a pseudo-random sequence. The averaged relative signed error for each target interval was calculated based on the participants' estimations. The six calculated signed errors, as well as the participant's age and gender were given as predictors for a linear regression model to determine the best predictors for the participants' MoCA scores using a backward method. The final regression model was found to be significant ($F(2, 33) = 5.06$, $p < .01$, $R^2 = 0.24$) using only two predictors of 6- and 10-second reproduction intervals. Our results show that the measures of working memory provide the most reliable associations with the variation of cognitive scores in older adults.

2-F -210 Optogenetic stimulation of VTA projections to the lateral nucleus accumbens shell increases maternal behaviors in rats.

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[1]Douglas Mental Health University Institute, McGill University, Montreal

The inputs of ventral tegmental area (VTA) dopamine neurons to the nucleus accumbens (NAc) shell are implicated in rewarding and motivational behaviors, including maternal behaviors. The mechanisms involved in the regulation of maternal behavior in NAc-related circuits are not well understood. In this study, we used in-vivo optogenetic techniques to parse the differences between the lateral and medial shell regions in influencing maternal behaviors. We found that the activation of lateral VTA-NAc shell projections significantly facilitated maternal behaviors when compared to both VTA-NAc medial shell activation and control groups. These findings indicate the potential for a unique role of the VTA-NAc lateral shell circuitry in regulating maternal behavior.

2-F -211 Correlated variability modifies working memory fidelity in primate prefrontal neuronal ensembles

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[1]McGill University, [2]University Medical Center Hamburg-Eppendorf, [3]Ottawa Hospital Research Institute, University of Ottawa

Neurons in the primate lateral prefrontal cortex (LPFC) encode working memory (WM) representations via sustained firing, a phenomenon hypothesized to arise from recurrent dynamics within ensembles of interconnected neurons. Here we tested this hypothesis by using microelectrode arrays to examine spike count correlations (rsc) in LPFC neuronal ensembles during a spatial WM task. We found a pattern of pairwise rsc during WM maintenance indicative of stronger coupling between similarly-tuned neurons and increased inhibition between dissimilarly-tuned neurons. We then used a linear decoder to quantify the effects of the high-dimensional rsc structure on information coding in the neuronal ensembles. We found that the rsc structure could facilitate or impair coding, depending on the size of the ensemble and tuning properties of its constituent neurons. A simple optimization procedure demonstrated that near-maximum decoding performance could be achieved using a relatively small number of neurons. These WM-optimized subensembles were more rsignal-diverse and anatomically dispersed than predicted by the statistics of the full recorded population of neurons, and they often contained neurons that were poorly WM-selective, yet enhanced coding fidelity by shaping the ensemble's rsc structure. Our results demonstrate that WM coding in LPFC neuronal ensembles arises from a complex synergy between single neuron coding properties and multidimensional, ensemble-level phenomena.

2-F -212 Chronic Toluene Exposure, Hippocampus-dependent Spacial Memory and Hippocampal Structure. Experimental Study

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Toluene and toluene-containing volatile substances are the most commonly abused solvents with a demonstrative addictive potential in humans. The central nervous system is one of the main targets: chronic toluene exposure is associated with long-lasting neurological, behavioral, neurochemical, and structural impairments. In the present study, we evaluate immediate and persisting effect of chronic toluene exposure on spatial memory and hippocampal structure in adult male Wistar rats. Each animal separately was exposed to toluene vapor (2000 ppm) or clean air for 3-5 min/d, during 20 d. Immediate effect of toluene chronic exposure was evaluated immediately after the end ofchronic inhalation, while persisting effect - 90 days after the end of toluene exposure. Impairment in spatial long-term memory was assessed using escape latency and Morris water maze test 24 h after training. Behavior in Water Maze comprise the acquisition and spatial localization of relevant visual cues that are subsequently processed, consolidated, retained and finally retrieved in order to successfully navigate and thereby to escape water. The hippocampus is a key structure for place learning, and the water maze procedures have been considered as a hippocampus-dependent. Therefore in parallel with behavioral studies, quantitaitve analysis of cell loss was performed in all layers of hippocampal CA1 and CA3 areas. The results revealed that in toluene-treated animals the long-term spacial memory in rats is worsened. Moreover, in both hippocampal areas significant loss of cells was observed in pyramidal

2-F -213 The Association between Filial Piety and Cognitive Impairment: Findings from a community-dwelling older Chinese population

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Background: Evidence suggests that prevalence of dementia in Chinese older adults will increase significantly over the next 30 years. This study aimed to examine the association between filial piety expectation and receipt and cognitive impairment among U.S. Chinese older adults. Method: 3,159 community-dwelling Chinese older adults in the greater Chicago area were interviewed in person from 2011-2013. Independent variables are expectations and receipts of filial piety from older adult's

perspective. Dependent variables were cognitive impairment as measured by MMSE, East Boston Memory Test, East Boston Delayed Recall, Digit Backwards and Symbol Digit Modality Test. Summary measured were constructed for global cognitive function. Result: Of the 3,159 participants, 58.9% were female and the mean age was 72.8 years. After adjusting for confounders, every 1 point lower in filial piety receipt was associated with increased risk for impairment global cognitive function (OR 1.07, 95% CI 1.03-1.11). Lowest tertiles of filial piety receipt was associated with greater risk for impairment in global cognitive function (OR 1.95, 95% CI 1.12-3.38). However, no statistically significant associations were found between filial piety expectations and global cognitive function. Discussion: This study suggests filial piety receipt to be an important risk factor for cognitive function impairment among U.S. Chinese older adults. Future longitudinal studies should be carried out to understand the temporal association between filial piety and cognitive function.

2-F -214 Global DNA Methylation Patterns in Perceptual Brain Regions of the Black-capped Chickadee (Poecile atricapillus)

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Black-capped chickadees (Poecile atricapillus) produce song to attract mates and defend territories, however song perception serves an equally important function, such as for individual recognition and mate choice. Songbirds have two main perceptual regions, the caudomedial nidopallium (NCM) and the caudomedial mesopallium (CMM). Previous research has focused on short-term neural changes in these regions in response to acoustic stimuli; however, long-term changes in these regions have not been investigated to the same degree. DNA methylation is one of several persistent epigenetic mechanisms that change the accessibility of DNA to be transcribed; increased levels of DNA methylation block transcription and can affect behavioural memory formation and maintenance. Our experiment attempts to understand the relationship between a bird's ability to discriminate among acoustic stimuli and levels of global DNA methylation in NCM and CMM. As part of another experiment, black-capped chickadees were exposed to one of two operant discrimination tasks using conspecific vocalization (the fee bee song). The birds experienced either an easy learning task or a hard learning task, and once the behaviour was established, the birds were sacrificed and their brains harvested. We adapted an immunohistochemistry protocol for mouse tissue to detect 5-Methylcytosine (5mC; a marker of DNA methylation) and NeuN--a neuronal marker. This study lays the groundwork for investigating acquired and heritable changes in DNA methylation at regulatory sites of genes involved in song perception and learning.

2-F -215 Synaptic levels of PKMζ in the BLA as a molecular marker of memory strength and incubation

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The atypical PKC isoform, PKMζ, is a persistently active kinase crucial for maintaining long-term memory. It actively prevents endocytosis of GluA2 subunit-containing AMPA receptors from the postsynaptic membrane. Stable long-term memories require an increased abundance of these GluA2 AMPA receptors while forgetting and amnesia have been associated with a loss of these receptors. Considering the importance of PKMζ in maintaining these AMPA receptors within the membrane, we investigated if PKMζ correlates with memory strength. We trained rats in an auditory fear conditioning protocol under naïve (one tone, no shock), weak (one tone-shock pairing), or strong (ten tone-shock pairings) conditions. Rats underwent a brief memory test 24 hours later and were sacrificed 24 hours following

this test. Levels of PKMζ within the BLA were quantified with Western blotting. Results show a strong correlation between PKMζ and performance at test. In another experiment, rats were tested 1 day and 30 days post-training and sacrificed 24 hours later. Western blotting revealed elevated levels of PKMζ in the BLA of rats sacrificed after this 30-day interval, suggesting memory incubation had occurred. These results provide a biological correlate of memory strength in the BLA that is sensitive to a continuous range of memory intensity. Furthermore, these results provide additional molecular evidence for the behavioural phenomenon of memory incubation.

2-F -216 USING AUTOMATED TOUCHSCREEN TASKS AS A HIGH-TROUGHPUT BEHAVIOURAL PLATFORM FOR DRUG DISCOVERY IN ALZHEIMER'S DISEASE

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[1]University of Western Ontario , [2]University of Guelph, [3]Baycrest Hospital , [4]Baycrest Hospital

he automated Bussey-Saksida touchscreen tasks have provided innovative ways to access cognition in rodents. The similarity with human tests, automation and potential for high-throughput suggest that this approach can revolutionize behavioural studies and facilitate drug discovery. We evaluated the performance of three mouse models of Alzheimer´s disease (AD) (5XFAD, 3xTG-AD and APP/PS1) to address the hypothesis that they may have common cognitive deficits that can be unmasked by touchscreen tasks. Males and females were tested longitudinally on 5-Choice Serial Reaction Time Task (5-CSRTT-attention), Pairwise Discrimination (PD-cognitive flexibility) and Paired Associate Learning (PAL-learning and memory). All data were verified using an automated quality control procedure and then entered into a large-scale open-access searchable database for mouse performance in these cognitive tests. Behaviour was highly reproducible between the two sites and between sexes. We detected attention deficits in both the 3xTG-AD and the 5xFAD mouse lines, but not in APP/PS1 mice. Overall, all the three mouse lines had no deficits in PD regardless of gender and age. Interestingly, all three mouse lines present deficits in PAL, suggesting that this task could be used to investigate disease-modifying therapeutics. Our approach will allow increased open access and sharing of standardized behavioural data between laboratories and highlights the potential use of behavioural assays in drug screening that can be adapted to a variety of diseases.

2-F -217 Novel Tabletop Navigation task used to show sex differences in spatial navigation

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Sex differences in spatial abilities have been reported in many mammalian species, including humans. The Morris Water Task (MWT) is an often-used behavioural assay of spatial ability in rodents that has been adapted to use in humans, typically as virtual reality. Such variations have lead some to theorize that males and females implement different strategies to solve spatial problems. On average, men tend to use cardinal directions, whereas women tend to use landmarks to solve these tasks. In our previous studies using the Real-World version of the MWT, we found superior male performance in the allocentric version, while a clear female advantage was observed in the egocentric version of the task. These findings led us to design allocentric and egocentric tabletop versions of MWT. We hypothesized that men would excel at the allocentric version where as females would excel in the egocentric version of the task. Sixty subjects (30 women) ages 18-25, were asked to locate a single, hidden target location in the allocentric condition over several trials with varying start locations. Male performance was

significantly better than females on this version of the task. A second experiment containing sixty subjects (30 women) ages 18-25, performed the egocentric version of the task. In the egocentric condition, women demonstrated a clear advantage compared to males. Together, these results indicate that although men and women can both solve spatial tasks, the default strategy is allocentric for men and egocentric for women.

2-F -218 Relations between event-related alpha perturbations and P300 in multiply concussed athletes

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Many studies have evidenced that concussions exert long-term and cumulative effects on brain function in asymptomatic athletes. Event-related potential (ERP) markers of attention and working memory, such as the P300 and the SPCN waveform components, were shown to be particularly vulnerable to recurrent concussions. In parallel, the impact of concussion on EEG power spectrum, and more particularly the alpha frequency band (8-12 Hz), showed persistent alterations even in asymptomatic concussed athletes. Interestingly, recent healthy control studies showed an association between event-related alpha activity perturbations (ERαP) and the P3 amplitude when performing visual attention tasks. Here, we investigated whether persistent alpha activity abnormalities in concussed athletes was related to amplitude reductions of the P3. In order to do so, we conducted ERP and spectral power analyses on EEG recordings collected when athletes performed a visual-spatial attention task. A total of 27 male football athletes (13 concussed, 14 age-matched controls) from a Canadian Varsity team were recruited for the purpose of this study. Both pre-stimulus alpha power and ERαP were strongly correlated with the altered P3 amplitude in the concussion group. Our data suggest that multi-concussed athletes exhibiting the worst alpha alterations were those with the most suppressed P3 component amplitude. This finding reaffirms the notion that ERαP and the P3 are neurophysiologically interrelated in the processing of target stimuli when performing a visual attention task, even in a clinical population.

2-F -219 Age of onset of obsessive-compulsive disorder predicts behavioural symptom severity in women during the perinatal period

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Background: Obsessive-compulsive disorder (OCD) is a heterogeneous psychiatric disorder, with sex and onset age differences. Women are at higher risk for exacerbation of obsessive-compulsive (OC) symptoms during the perinatal period, where new symptoms focused on the fetus/newborn may emerge. We explored whether age of onset was a predictor of OC symptom severity and mood during the perinatal period. Methods: 18 women with pre-existing OCD, including comorbid depression, were seen during 2nd-3rd trimester of pregnancy and 3-6 months postpartum. Behavioural measures collected at each time point included the Perinatal Obsessive-Compulsive Scale (POCS), Y-BOCS, EPDS and STAI. Onset age was defined as age at symptom presentation. Linear regression models examined whether onset age predicted behavioural symptoms, with age and depression comorbidity as covariates. Results: Onset age was a significant predictor of perinatal OC symptom severity in postpartum only, $p=0.01$, $R^2=0.44$. During pregnancy, onset age predicted depression scores, $p=0.01$, $R^2=0.42$, and state anxiety scores, $p=0.003$, $R^2=0.53$, but not trait anxiety. It failed to predict non-perinatal OC severity, as well as anxiety or depressive scores postpartum. Conclusion: Onset age was found to predict severity of some symptoms in the perinatal period. Specifically, earlier onset age was associated with increased state anxiety and depression scores in pregnancy and more severe perinatal OC symptoms postpartum.

Women with an earlier OCD onset age may be more vulnerable to worsened behavioural symptoms in the perinatal period.

2-F -220 The effects of chronic high fructose corn syrup pre-exposure on oxycodone-induced reward, locomotion, and dopamine concentrations in the nucleus accumbens

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Objective: There is evidence that sugar acts on the brain reward system similarly to drugs of abuse. This predicts that sugar and drugs should interact at both neural and behavioral levels. Hence, we examined whether rats pre-exposed to high fructose corn syrup (HFCS) would display a sensitized response to oxycodone(OXY) reward, OXY-induced locomotion, and OXY-induced elevation in dopamine (DA) concentrations in the nucleus accumbens (NAc). Methods: Male Sprague-Dawley rats received: 0%-24h/day, 50%-12h/day, or 50% -24h/day HFCS for 26 days. After a 9-day sugar free period, rats were tested on one of the following:(1)place conditioning with pre-test, conditioning (0, 0.16, or 2.5 mg/kg OXY), and test of preference; (2)locomotor sensitization involving context-dependent treatment with OXY (0, 0.16, or 2.5 mg/kg SC) over 5 days, followed by assessment of locomotor activity in the previously drug-paired context; (3)in vivo microdialysis of extracellular DA in the NAc following an acute injection of OXY (0 or 2.5 mg/kg SC). Results:It was found that 0.16 and 2.5 mg/kg OXY produced a place preference, but this was not significantly modified by HFCS pre-treatment. Furthermore, HFCS pre-treatment did not alter OXY-induced and context-induced locomotion. The results of microdialysis are being analyzed. Conclusion:Chronic HFCS pre-exposure did not alter OXY reward or psychomotor responses to OXY injections. Awaiting microdialysis data, it is concluded that the nature of sugar-drug interactions is more complex than believed and may depend on the type of sugar and drug of abuse tested

2-F -221 Dopamine in Ventral Tegmental Area Modulates Learning About Redundant Cues

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Learning about predictive relations is determined by the discrepancy between real and expected outcomes, named prediction-error. The blocking paradigm exemplifies the role of prediction-error on learning. In blocking, learning about the predictive relation between a cue (e.g., a tone) and an outcome (e.g. footshock) is impaired when this learning takes place in the presence of a good predictor (e.g. a light) for the same outcome. Here the light generates a small prediction error and thus blocks learning about the tone. This is contrasted to a behavioural control condition in which the tone becomes a good predictor for shock delivery when trained in the presence of a light that has not history of shock delivery, and thus allow for maximum prediction-error. Dopamine in the ventral tegmental area (VTA) has been implicated in reward prediction-error. Whether a similar role can be attributed to VTA dopamine in learning about fear remains unknown. We used the fear blocking paradigm to show that optogenetic activation of dopamine neurons in the VTA at time of expected shock further hinders learning about the blocked cue, therefore, augmenting the blocking effect in the aversive setting. Our results also indicate that optogenetic activation of dopamine does not modulate learning in the behavioural control conditions. Thus, our findings suggest that dopaminergic neurons in VTA are involved in modulating fear conditioning and predictive learning via a valance-specific prediction-error mechanism. Keywords: prediction-error, fear conditioning, dopamine, optogenetics

G - Novel Methods and Technology Development

2-G -222 The Odour Plus Maze: A new behavioural test of odour preference in mice

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Social and non-social olfaction are an important aspect of cognition for rodents. Despite this, there are limited behavioural tests available to assess approach or avoidance to odour cues. We have developed a one-trial test that can simultaneously assess rodents' behavioural response to a maximum of four different odours. Using male and female C57Bl/6J and B6129SF2/J mice, we compared odour investigation in our newly developed Odour Plus Maze, and in the two-choice Odour Preference Task that has been used previously to assess odour preference in rodents. We found that the Odour Plus Maze is more sensitive to differences in odour preference than the two-choice Odour Preference Task. Both male and female B6129SF2/J mice showed preference for odours from familiar versus unfamiliar mice in the Odour Plus Maze, but this preference could not be detected using the two-choice Odour Preference Task. In addition, both male and female C57Bl/6J and B6129SF2/J mice showed avoidance of a non-social odour in the Odour Plus Maze, but avoidance of this non-social odour was not detected in female C57Bl/6J mice in the two-choice Odour Preference Task. We propose that the Odour Plus Maze is a flexible, fast way of assessing odour preference in mice.

2-G -223 Nonlinear Model of a Nonlinear System: An Alternative view of fMRI Modelling

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The human brain is a manifestly nonlinear system; however, almost all methods currently used for the analysis of functional magnetic resonance imaging (fMRI) data focused on modelling linear relationships (e.g., Pearson correlation and the GLM). Linear methods have unquestionably made significant contributions, but a tool capable of describing nonlinearities within the system may provide new insight. Genetic programming, a type of artificial intelligence where the computer writes its own programs, is used to perform symbolic regression -- a model free type of regression analysis. With symbolic regression, the programs being written are mathematical expressions describing the relationships within data. Symbolic regression is data driven and makes few assumptions about the data. Unlike the general linear model which optimizes parameters for a strict linear model, symbolic regression optimizes both parameters and the structure of the model itself. fMRI data from the Human Connectome Project for thirty subjects performing all available tasks were segmented into meaningful regions of interest. Genetic programming was able to generate accurate nonlinear models describing the functional relationships between the regions of interest. The nonlinear models' accuracy was never statistically worse than the linear models', however the nonlinear models were much more succinct and contained novel relationships within the data that could not possibly have been found with traditional linear methods.

2-G -224 Evaluating hydrophobic microgel polymers for the intranasal delivery of haloperidol to the brain

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The blood brain barrier (BBB), a highly stringent barrier, prevents admission of many small hydrophilic and nearly all large molecules in circulation. The olfactory route, via the nasal cavity, offers possibility for brain targeting of pharmacological agents. Although, most novel neurotherapeutics, due to inadequate

aqueous solubility, will require a vehicle delivery system to accommodate this limitation. This study investigated the utilization of microgel (MG) polymer-based formulations to entrap haloperidol (HP), a typical antipsychotic drug commonly used to treat schizophrenia. We explored the potential of this formulation on targeting HP following intranasal (IN) administration to rats. We assessed the potential of 2 structurally different MG polymers (MMA and BMA) in their ability to entrap and efficaciously deliver HP. These formulations were delivered through both IN and intraperitoneal (IP) routes and behaviourally assessed for catalepsy (30, 60, 90 minutes post-administration) and locomotor suppression. Drug loading was found to be higher in MMA formulation than BMA. IN route was demonstrated to be more effective in early catalepsy induction as well as having a long lasting effect than IP route. Significant locomotion suppression was observed following both IP and IN administration of HP-loaded formulations. These results demonstrate efficacy of HP-loaded MG polymer via nasal route and its potential for drug to brain targeting with non-invasive administration.

2-G -225 In vivo label-free microscopy to infer nerve fibers morphology and myelination in health and disease.

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Understanding mechanisms of neurodegenerative diseases, developing effective diagnostic strategies and comparing treatment methods often require the investigation of nervous system cells morphology. Widely used magnetic resonance imaging techniques constantly report new alterations of white matter in various brain regions. Although very successful, these techniques lack the resolution to infer myelin integrity at the cellular level. Recently demonstrated Coherent anti-Stokes Raman Scattering (CARS) microscopy has accomplished cellular level, label-free imaging of myelin sheaths in the nervous system. However, a quantitative morphometric analysis of nerve fibers still remains a challenge. In this work, we developed an automated myelin identification and analysis method that is capable of providing a complete picture of axonal myelination and morphology at the microscopic scale in vivo. We applied this method to monitor lesions development and progression in the animal model of multiple sclerosis. We demonstrated that our approach provides more accurate description of the nerve fibers and allows the identification of subtle differences in myelin organization in vivo. This is especially useful for clinical and comparative studies, and may greatly enhance the understanding of nervous system organization and function.

2-G -226 Development of a Standardization Phantom for Measuring Brain Gamma-aminobutyric acid (GABA)

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γ-aminobutyric acid (GABA) is the most prevalent inhibitory neurotransmitter in the brain. Due to its importance in both normal brain function and in disease, there is considerable interest in reliable non-invasive measurements in vivo. The concentration of GABA is significantly lower than other dominating metabolites and is obscured by more abundant co-resonating metabolites such as creatine, glutamine and glutamate. Thus, the purpose of this study was to develop a proton magnetic resonance spectroscopy (1H-MRS) phantom for the standardization of GABA with the goal of long term quality assurance (QA) measures. A spherical design was implemented using metabolite spheres embedded in agar, with 2 concentrations of GABA; 1mM based on the average concentration in cortical grey matter and 2mmol to improve the resolvability of GABA. Single voxel spectra were acquired and fitted using Tarquin. Statistical analysis indicates that there is a difference in concentration within a session as well

as between sessions. This can be caused by a number of factors, such as B0 and B1 inhomogeneity. The phantom has promise as an option for long term QA, and future work will assess both B0 and B1 differences over time and how these affect GABA consistency. It is important to have a QA protocol for the detection of GABA to allow for performing multi-centre and longitudinal subject studies to determine the role of GABA and its subtypes in normal brain function, neuropathology, neuroplasticity, and aging. This will let 1H-MRS to be an important tool in the field of neuroscience.

2-G -227 Quantitative phase-digital holographic microscopy: Development of a customizable and multimodal imaging platform to uncover label free biomarkers of Psychiatric Disorders

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Multi-day tracking under the microscope of life cells such as neurons over a few days is extremely difficult due to cytotoxicity and phototoxicity particularly as far as staining processes are used. Thus, we have developed a label-free quantitative phase-digital holographic microscopy (QP-DHM), that allows real time non-invasive measurements, with a nanometric axial sensitivity, of cell structure and dynamics. Practically, QP-DHM allows to calculate from the quantitative phase signal a wide variety of cell parameters with a high-throughput screening capacity, including absolute volume, membrane fluctuations at the nanoscale, biomechanical properties, transmembrane water permeability and current, etc. in several cell types including neurons. It thus represents an appealing imaging modality to identify specific cellular phenotypes which can represent cellular biomarkers of diseases with relevancy to explore underlying pathophysiological processes. We are now focusing on combining QP-DHM with Induced Pluripotent Stem cells (iPSC) technology to identify new, original optical cellular phenotypes reflecting the neurodevelopmental component of major psychoses, including schizophrenia, bipolar disorders and major depression disorder. Here we report the development of customizable 3D-printable flow chambers and functional add-on of multi-wavelength, epi-fluorescence microscopy and electrophysiology to DHM. This upgrade of QP-DHM to a customizable and multimodal imaging platform will be used to study (IPSc)-derived neurons obtained from families heavily burdened with major psychoses

2-G -228 Development of a platform for an automated high-throughput analysis of central and enteric nervous systems in a mouse Parkinson's disease model

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The automation of the morphometric analysis of biological tissues makes it possible to carry out quantitative analysis at very high speed in whole tissues in order to identify, for example, pathophysiology in the brain. Recently, we developed a new automated morphometric method with MATLAB environment, which consists of an algorithm capable of recognizing areas on tissue and counting them. This software has been initially developed for lung morphometric analysis, and is currently being transposed for gut analysis in Parkinson?s disease model. Gut samples from adult wild-type and thy1-alpha-synuclein transgenic mice were collected. Distal ileum was microdissected and tyrosine hydroxylase (TH) positive neurons and alpha-synuclein were labelled by immunofluorescence. Slides were imaged using a whole slide scanner. At first, for validation purpose, dopaminergic neurons were counted manually on virtual slides. Thereafter, we modified our algorithm to segment and detect TH neurons and then to compare the results with the manual counts. In order to automate the process

to the maximum, we created four modules in MATLAB environment to achieve 1) format conversion and data extraction; 2) whole image pre-processing; 3) whole image segmentation, object detection, quantification, and visual representation. We improved the program by making parallel calculation instead of serial calculation and adding a function to indicate the level of work completion. Our workflow has been successfully validated on lung samples, and needs some extra optimizations to be fully operational for neuros

2-G -229 Fiber-based Tissue Identification for Electrode Localization During Deep Brain Stimulation Neurosurgery

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Deep brain stimulation's effectiveness relies on the ability of the stimulating electrode to be properly placed within a specific target area of the brain. Optical guidance techniques that can increase the accuracy of the procedure, without causing any additional harm, are therefore of great interest. We have designed an affordable optical fiber-based device that is small enough to be placed within commercially available DBS stimulating electrodes' hollow cores and that is capable of sensing biological information from the surrounding tissue, using low power white light. With this probe we have shown the ability to distinguish white and grey matter during stereotactic DBS lead implantations on both ex-vivo non-human primate intact heads, as well as on in-vivo non-human primates. The in-vivo measurements allowed us to compare simultaneously acquired optical data and neuronal activity using microelectrode recordings. We are in the process of further validating this procedure on other ex-vivo and in vivo primate specimens undergoing DBS electrode implantation. Using this data in combination with Monte Carlo light propagation simulations, we will show that we can localize the electrode within the brain, in real time. The end goal will be to deploy this technology during deep brain stimulation neurosurgery in humans, leading to an increase in the accuracy and therefore efficacy of the procedure.

2-G -230 A Bessel beam two-photon light sheet microscope with a large field of view and a high resolution for large-scale 3D brain imaging

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Recent advances in tissue clearing have made possible high-throughput imaging of large tissue samples such as the entire mouse brain. However, the challenge remains to image these specimens with high-resolution to get sufficient anatomic details. Here, we created a field of view, high-resolution light-sheet microscope to perform high-resolution whole brain 3D images in record time. A light sheet is obtained by scanning a long thin Bessel beam into the sample while a camera, placed perpendicularly to the scanning plane, captures the emitted two-photon fluorescence. Using a scanned Bessel beam, the axial resolution remains constant over the entire field of view, yielding a high isotropic resolution. Producing a light sheet with sufficient energy remains challenging. That is why we use of a regenerative-amplifier laser, which produces pulses with hundreds times more photons compared to conventional pulsed laser used in two-photon microscopy. The new light-sheet microscope was successfully used to obtain a 3D map of dopaminergic neurons in clarified mouse brains, with an axial resolution as high as 2um.The combination of our light-sheet technology with optical clearing promises to transform our ability to understand the neuro-circuitry of the brain and thus significantly advance understanding of neurological and psychiatric diseases which involve remodeling of brain connections.

2-G -231 Developing Technologies for Whole-Brain Functional Mapping in Behaving Larval Zebrafish

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The rapid development of technology to monitor and manipulate the activity of individual neurons throughout the brain offers a unique opportunity to study the neural circuits underlying behaviour. However, designing and implementing these tools can be challenging, as even the most fundamental behaviours require the coordinated activity of many neurons dispersed throughout multiple brain regions. The goal of our research is to develop whole-brain functional mapping technologies to study the neural circuits underlying visually-guided behaviours of larval zebrafish. We are designing a custom closed-loop behavioural feedback assay consisting of live video tracking integrated with dynamic closed-loop visual stimulation to determine the precise relationship between distinct visual features and discrete tail kinematics. We are also developing tools for recording tail kinematics during visual stimulation while simultaneously performing whole-brain two-photon calcium imaging. Both platforms will be designed in a manner to integrate the use of optogenetic actuators. These techniques should allow us to identify the precise functional connections between individual neurons. Furthermore, implementing these technologies will further assist in bridging the gaps between individual neurons, neural circuits, and behavioural outputs.

2-G -232 RoMon: An open-source web-based solution for rodent behavioural training and monitoring.

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Rodents have been the most widely used models in neuroscience and behavioural research. Measuring behavioural and physical phenotypes in animals in their home-cage environment is important for assessing the effects of experimental manipulations. Further, understanding the neural mechanisms underlying higher-order cognitive processes such as decision making, motor skill execution, perceptual discrimination, etc. requires training of animals in well-controlled tasks. Most of the commercially available solutions for automated animal training and monitoring are expensive and usually lack the flexibility to tackle broader experimental conditions. Here we present an open source automated web-based solution developed using a Raspberry Pi (RPi) for monitoring behaviour in a rodent model.The advantage of using a RPi is that it is a low cost (35$), credit-card sized computer that controls the data acquisition and experimental conditions. Our system is designed to simultaneously combine behaviour monitoring in multiple animals and brain activity recordings (i.e. brain imaging and electrophysiology). The automated and systematic implementation of training protocols with simultaneous monitoring of animal behaviour within the animal's home-cage dramatically reduces the efforts involved in animal training and data acquisition while also removing human errors and biases from the process. Further, our system is available to the research community as open-source, which will facilitate the creation of new research avenues in behavioural neuroscience using a low-cost open-source platform.

2-G -233 Probing neuron mechanics with a micropipette force sensor

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High throughput biological force measurements are essential to understanding the mechanisms underlying neuronal growth and elongation. However, large-scale experimental repetition is limited in most conventional techniques that probe force scales relevant to neurons. Here we use advances in micromanipulation techniques and real-time particle tracking to develop a novel approach to systematically study neuron mechanics. Our multi-purpose platform is a force sensor that can precisely control and manoeuver neurite-tethered polystyrene beads. We use a mechanical probe composed of a hollow micropipette with its tip fixed to a functionalized bead to incite the formation of a neurite in a sample of rat hippocampal neurons. We then move the sample relative to the pipette tip, elongating said neurite while simultaneously measuring its tension by optically tracking the beaded tip. This platform also allows the release of beads, enabling high throughput measurements. Moreover, this technique enabled us to investigate viscoelastic parameters of neurons, ultimately opening the door to answering fundamental questions about neurite regeneration and developing treatment strategies for nerve injury or neurodegenerative disease.

2-G -234 Fractal Dreams: Exploring differences in EEG signal scaling properties in individuals with high versus low dream recall

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Numerous neurophysiological processes exhibit power-law scaling. The 1/f -type spectral power decay has been observed in neuronal spiking frequency, EEG, MEG and fMRI signal fluctuations at multiple temporal and spatial scales. Here we explore the scaling properties in EEG sleep data using two formalisms: (I) the Wavelet Leader-based Multifractal formalism, in which the multi-fractal spectrum is used to estimate two scaling parameters denoted C1 (self-similarity) and C2 (multifractality) (ii) Detrended Fluctuation Analyses (DFA) in different frequency bands. We hypothesized that these measures may differ across sleep stages and potentially across subjects with high vs. low dream-recall. Our results reveal significant modulations of scaling parameters across sleep stages. More interestingly, machine learning analyses suggest that the multi-fractal scaling parameters differ across dreamers and non-dreamers and allow for significant decoding of high vs low-dream recallers. Whether these differences across individuals are related to their capacity to recall dreams, or to generate them, is an open question.

2-G -235 Quantitative approach to analyse protein expression in the brain of aged mice.

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In the human brain, each one of the 80-100 billion neurons connect to individuals neurons via an expected total of 100 trillion synapses to generate functional network implicated in various brain activity such as behaviour and cognition. Thus, it is foreseeable that normal aging can alter cellular and molecular mechanisms that routinely control neuronal homeostasis and function. In this context, our study aimed at uncovering how aging impacts the expression of various proteins found at excitatory synapses. To reach our goal, we performed brain subcellular fractionation on 7 and 22 months old mice. Proteins from each fraction were resolved on SDS-PAGE before performing quantitative western blots for glutamate receptors subunits and other various other targets of interest such as cytoskeleton, anchoring and synaptic proteins. Generally, less than 10 µg of total proteins give the required chemiluminescence linear dynamic range for the quantitative western blot detected with an imaging system. Unfortunately, our analysis did not revealed any significant changes in protein expression within

any of the compartments tested including the postsynaptic density of aged mice. However, our study exposes that western blots are a reliable and powerful technique when critical considerations are taken such as considering the expression level of a target of interest in a specific subcellular compartment of the brain. Importantly, our study highlights that western blot can deliver critical insights on how molecular determinants can be involved in the development of brain disorders.

2-G -236 A MACHINE LEARNING METHOD TO INVESTIGATE THE EFFECT OF FOCUSED ULTRASOUND ON GLIAL ACTIVATION

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Magnetic resonance imaging-guided focused ultrasound (MRIgFUS) is used for non-invasive and controlled drug delivery across the BBB in a temporal (6- to 12-hours) and localized manner. Some studies report that FUS treatments can activate microglia and astrocytes. The differences observed between studies can derive from differences in FUS parameters, and the spatiotemporal sampling methodology. In some contexts, microglia and astrocyte activation can be inhibitory and prevent regenerative processes including adult neurogenesis. Previous work from our lab has demonstrated FUS promotes a regenerative environment, and induces hippocampal neurogenesis. We hypothesize that neural stem cell (NSC) proliferation increases in the presence of glial activation. We developed a machine learning protocol to provide an unbiased analysis, through morphological and fluorescence measures to analyze the spatiotemporal activation of microglia and astrocytes in immunohistochemistry stained tissue. We then compare this activation timeline with a time course analysis of NSC proliferation. We show that microglia activation occurs by 1D post FUS and is largely resolved by 10D post FUS. Astrocytes show mild activation by 1D post FUS and remain activated by 10D post FUS. Neither astrocyte nor microglia activation is correlated with NSC proliferation. Furthermore, neuronal cell death was not observed following FUS. We conclude that following FUS both microglia and astrocytes are activated, and suggest that, based on NSC proliferation, glia activation does not inhibit a regenerative environment.

H - History, Teaching, Public Awareness and Societal Impacts in Neuroscience

2-H -237 The ethical and social impact of public discourse about fetal alcohol spectrum disorder: Key stakeholder perspectives

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Objective: To understand the views of key stakeholders on Canadian media coverage of fetal alcohol spectrum disorder (FASD), a neurodevelopmental disability that affects at least 1 in 100 Canadians. Limited research has explored their lived experiences, which we plan to address. This poster will report on our preliminary results. Background: Fetal alcohol spectrum disorder (FASD), a complex and heterogeneous diagnosis, results from prenatal alcohol exposure. Although Canadians are aware that FASD exists, and that drinking alcohol when pregnant can harm a fetus, they are less informed about what FASD entails. The media, a common source of information, could, in part, shape the way the public understands this disability, which often presents with no identifiable physical features. In addition, media discourse could be a factor in the generation of stigma towards people with FASD, and women who drink while pregnant (i.e., in the latter case, due to mother blame and shame) - especially given the

media's history of poorly portraying people from marginalized groups. Methods and preliminary results: We are conducting semi-structured focus group interviews with three stakeholder groups: 1) adults with FASD; 2) adoptive parents of people with FASD; and 3) healthcare professionals with experience caring for people affected by FASD. We will report preliminary data with respect to important issues such as 1) diagnosis; 2) stereotypes and stigma; and 3) participant reactions to examples of media content about FASD.

2-H -238 BrainReach/Mission: Cerveau : Bringing Neuroscience to the Montréal Community

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BrainReach/Mission: Cerveau is an award-winning, non-profit, bilingual community outreach program designed to promote science education in French and English public schools in Montreal. Brain Reach is managed by a committee of graduate students from the Integrated Program in Neuroscience at McGill University. BrainReach provides neuroscience-based workshops to under-resourced public schools through our Elementary (E) and High School (HS) divisions, targeting Grade 4 and Secondary 3 (Grade 9) classes, respectively. In the 2015-2016 academic year, we served 24 schools (17 E, 7 HS), reaching some 1100 students (730 E, 370 HS). Our educators lead 60-minute interactive workshops over six or eight months, covering grade-appropriate topics, such as brain and neuron anatomy, localization of function, and neurophysiology. BrainReach thus nurtures a relationship between graduate and public school students by meeting the following goals: (1) expanding science education in while integrating into the mandated curricula; (2) inspiring students to engage in STEM fields by exposing them to neuroscience and the broad diversity of neuroscience researchers; and (3) providing an avenue for budding researchers to engage in community involvement. We use an evidence-based approach increase the quality and delivery of our program for current and future students by obtaining feedback in the forms of questionnaires and surveys routinely administered to students and teachers at participating schools as well as to our own volunteers, and integrating this feedback into our workshops.

2-H -239 Increasing Research Value With Sex-Specific Reporting of Data: The Cholinesterase Inhibitor Example

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Drug trials routinely collect data on sex, yet seldom report results separately by sex, and thus cannot inform our understanding of differences between women and men on the benefits and harms of drug therapy. Consequently, valuable data are wasted, resulting in a missed opportunity to increase research value. We aimed to quantify this gap by examining drug trials of cholinesterase inhibitor (ChEI) therapies for dementia, a condition which affects more women than men. A systematic review was performed of randomized controlled trials (RCTs) of oral formulations of ChEIs (donepezil, rivastigimine or galantamine) with clinical outcomes. Sex-specific data were extracted from eight sections of each article. For donepezil trials, the most widely used ChEI, detailed data on adverse events were obtained. In all, 33 RCTs were evaluated with 15,971 participants in total, of which 57% were women. These RCTs were highly cited and published in high impact journals. In the title, introduction, limitations and conclusion sections, no article mentioned sex. In the abstract section, 3 (9%) articles mentioned sex as a demographic characteristic. In the methods section, 6 (18%) articles mentioned sex. For the results

section, almost all 32 (97%) trials mentioned sex, all as a demographic characteristic in a table. In donepezil trials, no trial provided sex-specific reporting of adverse events. Through this analysis, we see an almost complete lack of sex-specific reporting of data in ChEI trials. Sex-specific reporting of data should be required in all trials to increase research value.

IBRO International Brain Research Organization

2-IBRO-240 Analysis of nmgp-1 Function in C. elegans

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Proteolipidic protein (PLP) family constitutes the myelin-related proteins, which are widely present in many species. This group includes the mammalian glycoprotein GPM6A. GPM6A is expressed in the central nervous system and participates in neuronal morphology such as neurite extension and filopodium formation. NMGP-1 is the functional ortholog of GPM6A and the only member of the PLP family in Caenorhabditis elegans. Although GPM6A interaction partners are unknown, there are several candidates, such as CORO1A, PAK-1, and MEF-2. To examine these possible interactions we developed a series of genetic tools such as a new strain neuronally sensitive to RNA interference (RNAi) with a deletion in the nmgp-1 gene. We examined the role of NMGP-1 in C. elegans neurons. For this, we performed RNAi in strains with neuron specific RNAi sensitivity to interfere nmgp-1 only in these cells. Interfering nmgp-1 in neurons diminishes egg laying, delays recovery time from resistant stress dauer state and increases lifespan. We investigated the NGMP-1 role in amphid sensory neurons morphology. These neurons allow the worm to sense environmental stimuli and regulate dauer state. To investigate possible alterations in the morphology of amphid neurons due to nmgp-1 deletion, we created a new strain expressing GFP in the amphid neurons ASJ and containing a deletion in the nmgp-1 gene. Altogether, the genetics tools and the phenotypes observed will help us to study the role of NMGP-1 at the level of whole organism and clarify cell signaling pathways in which NMGP-1 participates.

2-IBRO-241 Dopaminergic signaling counteracts cognitive deficits and depressive-like behavior in Alzheimer's disease models

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Alzheimer's disease (AD) is a common form of dementia, affecting more than 35 million people worldwide. Soluble oligomers of the Aβ peptide (AβOs) accumulate in AD brains and are known for mediating synapse damage and memory loss in animal models, and are increasingly regarded as proximal synaptotoxins in AD. Physiologically, dopamine modulates memory and synaptic plasticity, but in the context of AD, its potential roles remain largely unexplored. Here, we report that dopaminergic signaling is impaired in in vitro and in vivo models of AD, and selective activation of dopaminergic D1 receptors (D1R) restores behavioral and synaptic deficits in such models. In cultured slices of both rodent and human brain cortex, exposure to AβOs resulted in loss of D1R-mediated cAMP production, and subsequent reductions in PKA activation, CREB phosphorylation and BDNF production. Activation of D1Rs in cultured neurons with a selective agonist, SFK38393, prevented binding of AβOs and ensuing synaptic loss. In APP/PS1 mice, chronic administration of SFK38393 restored memory function and LTP. We further show that bupropione, a dopamine reuptake inhibitor, restores non-cognitive behavioral deficits, including depressive-like behavior and social isolation; important features of the disease,

reproduced in different mouse models of AD. AD and major depressive disorder are highly prevalent neuropsychiatric conditions with intriguing epidemiological overlaps. Understanding the role of dopamine in AD may help connect different aspects of the disease, and provide novel targets for therapy.

2-IBRO-242 Protective effects of cannabidiol against seizures, neuronal death and glial proliferation are modulated by the enzyme PI3K gamma

Isabel Vieira de Assis Lima[1], Edleusa Marques Lima Batista[1], Ivan Lucas Brandao[1], Paula Maria Quaglio Bellozi[1], Fabiola Mara Ribeiro[1], Fabricio de Araujo Moreira[1], Antonio Carlos Pinheiro de Oliveira[1]
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Introduction: Cannabidiol (CBD) has anticonvulsant properties in rodents and humans, but its mechanisms of action are not completely known. Thus, the present study aimed to investigate the involvement of the enzyme phosphatidylinositol 3-kinase gamma (PI3Kγ) in the neuroprotective and anticonvulsant effects of CBD. Methods: Neuronal hippocampal cultures were prepared from hippocampus of C57Bl/6 (WT) and PI3Kγ-/- neonatal mice. The WT cultures were pre-incubated with CBD (0.1, 1 or 10 µM) or with a PI3Kγ inhibitor (AS605240 - 0.01 µM) followed by CBD (0.1 µM); the PI3Kγ-/- cultures were pre-incubated with CBD (0.1 µM). Cultures were incubated for 4 h with glutamate (50 µM) or vehicle to evaluate cell death. Adult male mice received CBD (30, 60 or 90 mg/kg, i.p., -1h), valproate (300 mg/kg, i.p., -30 min) or vehicle followed by a bilateral intrahippocampal injection of pilocarpine to induce SE. Seizures were classified according to the Racine scale. After 24 h, the animals were perfused and their brains processed, for further histological techniques to evaluate neuronal death, microglia and astrocyte staining. Results: CBD reduced cell death induced by glutamate in all concentrations tested in vitro and in vivo. However, pharmacological or genetic inhibition of PI3Kγ reduced the neuroprotective effects of CBD. Besides, CBD decreased the severity of SE, microglial and astrocytic activation in all doses tested, although these effects were not observed in PI3Kγ-/- mice. Conclusions: The neuroprotective and anticonvulsant effects of CBD may be dependent on PI3Kγ activity.

2-IBRO-243 Neuroprotective cell therapy in a sporadic Alzheimer rat model

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Alzheimer's disease (AD) is the most common dementia. Our objective is to develop therapeutic strategies that allow preventing and/or overcoming the degenerative changes in AD. In this context, cell therapy emerges as a promising therapeutic approach. We explored the therapeutic effect (after 24 days) of human mesenchymal stem cells (hMSC) in an AD rat model by intracerebroventricular (icv) injection of streptozotocin (STZ). Intact, STZ and STZ+MSC groups were used. STZ and STZ+MSC groups received 3 mg/kg STZ-icv and, 24 hours later, the STZ+MSC group received 2x10^5 MSC-icv. STZ+MSC group showed a significant improvement in learning and spatial memory by the Barnes Maze (BM) and recognition memory by Novel Object Recognition test (NOR). We also assessed the effect of intravenous (iv) administration, as a non-invasive route, of hMSC on behavior and microgliosis in the dorsal hippocampus of AD rat model. Intact, STZ and STZ+MSC groups were used. After 24 days of STZ, when the damage was already established, animals received four times 1x10^6 MSC iv. We performed Open Field (OF), NOR, BM and Marble Burying (MB) tests to estimate memory, depression-like and anxiety-like behaviors. STZ group showed an increase in Iba1-immunoreactive microglial cells and a deficiency in

all behavioral tests. STZ+MSC group improved its performance in OF, BM and MB. We concluded that MSC therapy is a suitable biological tool in neurodegenerative disorders, preventing the progression of cognitive impairment when injected in situ or restoring it when systemically administered for two months.

Wednesday, May 31, 2017

A - Development

3-A -1 Prenatal Valproic Acid Exposure Reduces Male Rodents' Sensorimotor Abilities, But Enhances Females' Abilities

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The prevalence of Autism spectrum disorders (ASD) in Canada has increased by more than 100% in the last ten years. ASD in humans is characterized predominantly by social deficits, but difficulties coupling perception and action may underlie the social deficits seen. Exposure to Valproic Acid (VPA) during pregnancy causes autism-like neurological changes in both rats and humans, and VPA exposure in utero in rats has been validated as an effective animal model of ASD. We evaluated the sensorimotor abilities in a rodent model of ASD with a modified staircase task. The Montoya staircase task tests rodents' ability to perceive a food reward (goal) and make successful goal-directed movements. We expected the staircase task to reveal perception to action deficits in the VPA exposed rats compared to saline controls, specifically in males. Performance was evaluated based on remaining pellets by amount and location within the apparatus. The VPA exposed males consistently took significantly fewer pellets than other groups and also ate fewer pellets, of those they took. In contrast, the VPA exposed females took and ate more pellets than any other group. This data supports our hypothesis, the VPA exposed males were less effective in reaching and grasping treat pellets, which is consistent with the literature on ASD development in humans. We propose the VPA-exposed males had trouble coupling perception and action, impeding their abilities in goal-directed movements.

3-A -2 Maternal immune activation and later-life behavioral deficits: Is there a link with embryonic microglia migration?

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An increasing number of non-inflammatory roles for microglia in normal neurodevelopment have been identified: microglia pattern the developing central nervous system (CNS) controlling the pool of neural progenitor cells (NPCs) as well as their differentiation and neuronal death. Moreover, recent studies revealed that microglial cells might be, to some extent, novel guideposts during embryonic forebrain wiring. Interestingly, these "developmental" cells originate from a unique wave of embryonic progenitors early on, and thus are present at all stages of brain development. Neurodevelopmental disorders have been repeatedly associated with developmental defects in forebrain wiring potentially caused by maternal immune activation (MIA). Using Lipopolysaccharide (LPS) as the immunogenic agent, we investigated the impact of an early MIA on the microglial migration process. Our rationale here is

that a delay or alteration of this migration could potentially have drastic consequences in altering developmental processes and result in a broad spectrum of developmental disorders. We characterized the impact of early maternal LPS on the number and phenotype of microglial cells and ultimately on the offspring's behavior relevant to neurodevelopmental disorders. Several behavioral deficits in progenies coming from dams having received LPS during pregnancy have been observed (communication deficits, repetitive behavior, social interaction abnormalities and social memory alterations), with a stronger effect of MIA observed in males.

3-A -3 Maternal high fat diet and its effect on offspring developing brain: implication for neurodevelopmental disorders

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The main lipid component of the brain is myelin which is produced by oligodendrocytes and coats neuronal axons insulating them for faster transmission. Myelination is a dynamic process that starts in the third trimester of pregnancy and notably requires crosstalk between oligodendrocytes and microglia - the brain resident immune cells. Proper myelination of axons is crucial for proper brain function and its alteration is a common feature of developmental disorders that include autism and schizophrenia. This process can be affected by a variety of environmental factors including dietary fat. Indeed, recent studies in rodents demonstrated that maternal high fat diet (mHFD) induces hypomyelination and neuroinflammation in the offspring. We investigated if mHFD could disrupt neurodevelopment by altering myelination leading to abnormal behaviors relevant to developmental disorders and whether this involves changes in microglial function. Female mice were fed with control or mHFD (60% kcal from saturated fat) for 4 weeks prior to mating and continued to litter weaning. Phenotypic characterization of the offspring was performed at adolescence (P30-40) and adulthood (>P60). The animals were sacrificed at P85 and, their blood and their brain collected for molecular analyses. Offspring from mHFD dams showed altered social and repetitive behaviors which were associated with molecular changes. Our study provides new insight on the impact of mHFD during development and its associated long-term effects.

3-A -4 Ancestral Stress Alters Lifetime Mental Health Trajectories and Cortical Neuromorphology via MicroRNA Regulation

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Recent studies have shown that ancestral stress may propagate to subsequent generations and program mental health trajectories in unexposed offspring. Here we investigated if exposure to prenatal stress in a single generation (transgenerational stress) versus repeated prenatal stress across generations (multigenerational stress) generates changes in emotionality, neuromorphology and epigenetic regulation in adult male and female rats. Male and female F1-F4 generations were derived from a rat lineage in which their ancestral mother (F0) or all mothers (F0-F3) were stressed during pregnancy. Young adult F1-F4 generation offspring were tested in an open field task and an elevated plus maze for anxiety-like behaviours, and stress reactivity. Golgi-Cox analysis was used to investigate neuronal morphology of medial prefrontal cortex (mPFC) and orbital frontal cortex (AID) and micro-RNA (miRNA) deep sequencing of frontal cortex to identify epigenetic regulatory pathways. Both stressed lineages were characterized by an altered affective state. Multigenerational stress exceeded the effects of transgenerational stress by increasing anxiety-like behaviours and altering stress responsiveness in adult male but not female rats. These functional and physiological changes were accompanied by long-term

alterations to dendritic branching and spine density of the prefrontal brain regions. Ancestral stress altered miR-221 and miR-26 expression in frontal cortices. Thus, programming by ancestral stress may determine mental health outcomes and neuroplasticity via epigenetic regulation.

3-A -5 Slitrk2 and Slitrk5 differentially control excitatory and inhibitory synapse formation on dopaminergic neurons and hyperactivity behaviour

Charleen Salesse[1], Julien Charest[1], Hélène Doucet-Beaupré[1], Paul De Koninck[1], Martin Levesque[1]
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Dopaminergic circuitry dysfunction is linked to the development of neuropsychiatric disorders, including attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). The transcriptional factors Lmx1a/b are essential for each step of midbrain dopaminergic (mDA) neuron development. We previously reported that Lmx1a/b conditional knockout (cKO) mice show ADHD and OCD-like behaviour. Here, we found that Lmx1a/b loss of function reduced dendritic morphology and frequency of miniature excitatory postsynaptic currents in mDA neurons. Gene expression profiling in Lmx1a/b cKO mice revealed that Lmx1a/b control the expression of Slitrk2 and Slitrk5, two members of the Slit and Trk-like (Slitrk) protein family. Gain and loss of function of Slitrk2/5 in cultured mDA neurons showed that dendritic growth is regulated positively by Slitrk2 and negatively by Slitrk5, while Slitrk2 promotes specifically functional excitatory synapses and Slitrk5 promotes functional inhibitory synapses. Reduced expression of Slitrk2 in mDA neurons of the VTA resulted in ADHD, whereas the reduced expression of Slitrk5 caused lower motor activity. To test if these behavioural effects arise from a change in mDA neuron activity, we chronically inhibited them during postnatal development using pharmacogenetics. This induced ADHD behaviour and reproduced some aspects of the Lmx1a/b cKO mice. Altogether, our results indicate that Lmx1a/b and Slitrk2/5 are key players of mDA neuron development and synapse formation, which may have an impact on ADHD and OCD-like disorders.

3-A -6 Impact of energy consumption and autophagy on neuronal migration

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Cell migration is a dynamic, ATP dependent process, essential for brain development. The dynamics morphological remodelling of migrating cells leads to formation of protein aggregates, organelle damage and plasma membrane leftovers. One of the catabolic intracellular pathways that maintain cellular homeostasis is autophagy. Here we evaluated the involvement of autophagy and its link to energy level in neuronal migration. We used rostral migratory stream of adult mice as a model system and found that autophagy-related proteins are present in 50% of neuroblasts. Time-lapse optical imaging of autophagosomes labeled with GFP-RFP-LC3 shows an active autophagic flux with an increase in density of autophagosomes during stationary phases. Pharmacological alteration of cell migration led to the changes in autophagy, and reciprocally, genetic impairment of autophagy in neuroblasts decreased the distance of cell migration because of an increase in the percentage of stationary periods. We observed the same deficit when AMPK, an energy sensor and autophagy activator, was blocked by CompoundC, suggesting an involvement of energy level in autophagy activation. We optically monitored energy consumption in neuroblasts, using PercevalHR, a ratiometric sensor of ATP/ADP. Our findings indicate a decrease in ATP/ADP ratio during migratory phases and an increase during stationary periods. This is consistent with the observed increase in autophagosomes density during stationary period, reinforcing the link between energy consumption and autophagy in cell migration.

3-A -7 CaMKIIa expression defines two functionally distinct populations of granule cells involved in different types of odor behaviors

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In the olfactory bulb, granule cells (GCs) represent a population of interneurons that play an important role in odor information processing. Based on the expression of neurochemical factors, several subtypes of GCs have been identified. However, the role played by these subtypes in olfactory processing and odor behavior remains unknown. Using in vivo two-photon calcium imaging we show that GCs can also be subdivided into functionally distinct subtypes, characterized by the expression or lack of Ca2+/calmodulin-dependent protein kinase IIα (CaMKIIα+). CaMKIIα+ cells are not distinguishable from their CaMKIIα- counterparts in terms of localization in the granule cell layer, dendritic arborization or spine density, but they receive weaker inhibitory inputs resulting in their preferential activation by incoming olfactory stimuli. Interestingly, 75-90% of GCs expressing the immediate early gene cFos in basal conditions were CaMKIIα+ GCs, a similar percentage being found after exposure to a novel odor or an odor discrimination task. On the other hand, perceptual learning resulted in an increased activation of CaMKIIα- cells. Pharmacogenetic inactivation of CaMKIIα+ GCs affected habituation/dishabituation odor discrimination performances but not perceptual learning. Altogether, our results suggest that CaMKIIα+ and CaMKIIα- GCs represent functionally different subpopulations of cells which play distinct roles in odor behavior.

3-A -8 Environmental programming of adult foraging behavior in the nematode Caenorhabditis elegans

Sreeparna Pradhan[1], Michael Hendricks[1]
[1]McGill University

Environmental influences during development can have long term effects on adult physiology and behavior. Adverse environmental conditions during early development have been linked to a number of adult-onset metabolic and psychiatric disorders. The short life-cycle, genetic tractability and the anatomical simplicity of the neuronal network makes the nematode Caenorhabditis elegans an ideal model organism to study environmental programming of adult behavior. Here we investigate how starvation at early larval stages affects developmental plasticity and alters adult behavioral traits. In response to starvation, C. elegans larvae may enter an arrested developmental stage, called dauer. We examined if the characteristic foraging behavior seen in C. elegans adults are changed in animals which experienced dauer in their developmental history. We established that post-dauer animals show reduced exploratory foraging behavior. This behavioral plasticity in response to early life stress is seen in wild isolates but not in the lab-adapted strain. Our current studies are exploring the neural correlates of this permanent change in behavior using calcium imaging. Initial findings indicate that dynamics of the interneuron circuitry regulating reversals in an animal?s trajectory is altered in post-dauers. Since nematodes share conserved genetic, metabolic and developmental pathways with mammals, this work will add to our understanding of developmental plasticity in response to environmental stress.

3-A -9 Acute hypoxia reveals a developmentally-inhibited pattern generator for lung breathing in pre-metamorphic tadpole brainstem preparations

Tara Janes[1], Jean-Philippe Rousseau[1], Stéphanie Fournier [1], Richard Kinkead[1]

[1]*Universite Laval*

In terrestrial vertebrates, the development and maturation of the respiratory central pattern generator (rCPG) must occur before pulmonary breathing is established. While the developmental processes governing rCPG maturation remain elusive, amphibians, which undergo pulmonary development during metamorphosis, offer a unique opportunity to study evolutionarily conserved rCPG's. Using L. catesbeianus (Bullfrog), our lab has sought to elucidate mechanisms of rCPG development and how environmental perturbations influence this process. Pre-metamorphic tadpoles utilize gill breathing as the lungs are rudimentary, and yet evidence exists that lung motor activity is functional at early stages. Our cranial nerve recordings from in vitro brainstem preparations confirmed that lung bursting indeed occurs in pre-metamorphic tadpoles (without forelimbs), but is depressed relative to post-metamorphic adults. As the impact of early environmental 'experience' on respiratory development has yet to be explored, we determined if acute hypoxia (10 min; 0-10%) altered lung bursting in pre-metamorphic tadpoles. This challenge increased lung burst frequency (~150%) and initiated lung activity in preparations expressing only buccal (gill) rhythms. Importantly, lung burst frequency persisted above baseline levels (~160%) beyond 3 hours following washout, suggesting long-term changes in respiratory networks. We hypothesize that hypoxia-induced, activity-dependent potentiation acts concurrently with suppressed inhibitory mechanisms to facilitate expression of adult-like lung motor patterns.

3-A -10 Genetic targeting of quiescent adult neural stem cells reveals their in vivo biological properties

Sandra Joppé[1], Loic Cochard[1], Louis-Charles Levros[1], Laura Hamilton[1], Anne Aumont[1], Karl Fernandes[1]
[1]*Université de Montréal*

Thousands of neurons and glial cells are born each day within the lateral ventricle walls of the adult mammalian brain. Neural stem cells (NSCs) can be isolated from the periventricular region and are responsible for this continuous generation of neural cells, but NSCs appear to be comprised of multiple distinct subpopulations whose individual properties and lineage relationships cannot be readily distinguished using current transgenic technologies. Here, we use an adult electroporation approach to specifically target and study ventricle-contacting GFAP-expressing cells, the putative quiescent NSCs (qNSCs) of the adult brain. We show that these ventricle-contacting GFAP+ cells only rarely divide, and following Cre-Lox mediated fate-mapping, only rarely produce neuroblasts or olfactory neurons even following extended periods. Intriguingly, this qNSC population also does not readily generate neurospheres, a property associated with the active NSC (aNSC) population, and exhibits limited reaction during AraC-induced niche regeneration. These data indicate that ventricle-contacting qNSCs only infrequently contribute to the aNSC population, supporting a model in which qNSCs and aNSCs are largely maintained as separate pools.

3-A -11 Stimulation of neighboring retinal ganglion cell inputs promotes axonal branch elaboration of an unstimulated retinotectal axon

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A major endeavour of developmental neuroscience is to uncover the precise rules that govern neural circuit formation. Here, we utilize the developing retinotectal system of albino Xenopus laevis tadpoles to elucidate how differential neuronal activity between neighbouring cells can alter axon remodeling. Using in vivo two-photon microscopy, we observed that visually evoked neuronal activity in many neighbouring retinal ganglion cell (RGC) axons increases the rate of dynamic branch additions in a single unstimulated axon, expressing tetanus toxin light chain fused to EGFP (TeNT-Lc:EGFP) to prevent it from

activating its postsynaptic partners. By contrast, when we visually stimulate a single TeNT-Lc:EGFP RGC, without stimulating the other neighboring inputs, we instead observed a cell-autonomous increase in the rate of axon branch retraction. Taken together, these results suggest that increased activity of neighbouring axons, presumably cooperatively acting to drive postsynaptic firing of tectal neurons, is sufficient to promote activity-dependent dynamic axonal branch remodeling and growth of a silent axonal input, whereas increased activity of a single input by itself that fails to activate its postsynaptic partner may enhance axonal pruning.

3-A -12 The role of microglia in the developing hypothalamus

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

The influence of microglia during CNS inflammation and injury is an active area of research. It is now appreciated that microglia actually begin to invade the developing brain around embryonic (E) day 10.5 in mouse, raising the interesting notion that these yolk-sac derived immune cells might play an unappreciated role in CNS development. Indeed, early reports suggest microglia can influence neurodevelopmental processes such as progenitor maintenance and cell differentiation. Here we explore the functional role of microglia during embryonic hypothalamic development. To date, we show that microglia invade the hypothalamus starting at E11.5 and align with ventricular progenitors near the end of neurogenesis and the onset of gliogenesis at E15.5, where they appear to be in a highly activated state. These data led to the hypothesis that microglia play an unappreciated role in controlling the timing of gliogenesis in the developing tuberal hypothalamus. To test this hypothesis, we employed a pharmacological knock-down model to eliminate microglia from the embryonic brain. The elimination of microglia led to a loss of astrocytes in the tuberal hypothalamus, suggesting microglia might influence progenitor cells to control astrocytogenesis. Indeed, using live cell imaging, we observed a fascinating and novel interaction between microglia and radial glia near the ventricular zone. Combined, we propose a novel mechanism whereby microglia interact with radial glia to control the timing of gliogenesis in the tuberal hypothalamus.

3-A -13 Sensitization of spinal motor neurons to Netrin1 by ephrin-A5

Louis-Philippe Croteau[1], Tzu-Jen Kao[2], Artur Kania[1]
[1]IRCM, [2]Taipei medical university

Axon guidance cues act in concert, but the molecular mechanisms underlying such interactions remain obscure. A subpopulation of limb-innervating axons of lateral motor column (LMC) motor neurons is attracted to Netrin-1 and repelled from ephrin-A5. We previously showed that Neogenin mediates LMC axon attraction towards Netrin-1 and that Netrin-1 and ephrin-A5 guide LMC axons synergistically. To gain insight into the mechanism controlling such synergy, we used fluorescence immunohistochemistry and enrichment for cell surface proteins, to show that ephrin-A5 stimulation results in an increase in Neogenin protein levels in LMC growth cones, and concomitant increase in Netrin-1 binding. This effect is enhanced by overexpression of the ephrin-A5 receptor EphA4, implicating ephrin-A:EphA signalling in increasing Neogenin at the growth cone. Surprisingly, the overexpression of EphA4 lacking its intracellular domain also enhances Neogenin levels. As functional evidence for the ephrin-A5 induced sensitization of LMC axons, we demonstrate that the bath addition of ephrin-A5 increases the outgrowth of LMC axons over Netrin-1 containing stripes. Our results suggest that ephrin-A5 may synergize with Netrin-1 in LMC axon guidance by increasing the levels of Neogenin receptors at the growth cone, leading to enhanced Netrin-1 signalling. Modulation of axon guidance responses to a

combination of cues may be an efficient way of diversifying guidance responses despite a limited variety of guidance cues and may be necessary for achieving complex circuitry.

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3-A -14 Sex and inhibition: sex-specific differences in the development of the hippocampal GABAergic network

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Sex differences in brain function underlie robust phenotypic and behavioral differences between males (♂) and females (♀). Sexual differentiation of the brain is influenced by testosterone secreted by the testes and its metabolites during the perinatal period. This same period is critical for the GABAergic network that undergoes structural and functional maturation. To determine if these inhibitory modifications have an effect on memory formation, ♂, ♀ and androgenized ♀ rats were evaluated using the Morris Water Maze test (MWM). To identify inhibitory synapses in the hippocampus of all sexes during postnatal days (PND) 3, 7 and 40, KCC2 was co-labeled with gephyrin using immunohistochemistry. Protein expression of KCC2 was evaluated in the same region of all sexes at the same ages using Western blot assays. MWM data showed no difference in the number of target crossings during the probe test suggesting equivalent learning capacities between all sexes. Preliminary qualitative data showed inhibitory synapses only at PND40. In addition, data at PND7, an age when sexual dimorphism has been shown in KCC2 expression, showed high levels in ♀ than ♂ although not statistically significant. Interestingly, KCC2 expression in androgenized ♀ seems to follow the same pattern as the expression in ♂. The study of the expression of proteins of the GABAergic system and their effect on the physiology and behavior in three different sexes will make it possible to know how testosterone affects the development of the inhibitory system within the hippocampus.

3-A -15 Heterogeneity of the blood-brain barrier

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

3-A -16 GABA SIGNALLING PROMOTES THE PROLIFERATION OF ADULT NEURAL PRECURSOR CELLS BY MODULATING CREB SIGNALLING AND REPRESSING NOTCH PATHWAY.

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Previous studies implicate GABA signalling in negatively modulating neural stem cell (NSC) activity within the embryonic and postnatal mammalian brain neurogenic niches, specifically the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus (DG). Using specific agonists and antagonists molecules, we show that GABA signalling increases adult SVZ neurosphere growth through GABA-A receptor. This positive regulation by GABA signalling on proliferation was also confirmed using inhibitors of Glutamate-acid decarboxylase (Gad65/67) and GABA transaminase (GABA-T), two enzymes involved in GABA metabolism. In vivo pharmacological and genetic manipulation of GABA signalling also increased the number of proliferative cells in the adult mice SVZ niche. Furthermore, GABA treatment on neurosphere cultures increased CREB phosphorylation and inhibited the expression of Notch target gene Hes5. Consistent with these results, analysis of Notch isoforms and of Hes1/5 promoters revealed the presence of CREB binding sites. We show by luciferase assay and immunocytochemistry that CREB-1/2 and a dominant active form of CREB-2 blocked Hes-1/5 promoter activity while the dominant negative form had a converse effect. Overexpression of GAD67 by in vivo electroporation in the lateral ventricle also repressed Hes1 activity while overexpression of KCC2 enhanced it. These results reveal a positive regulation of adult neural precursor cell proliferation by GABA signalling, potentially mediated by modulating CREB activity and repressing the Notch pathway.

3-A -17 A role for the calcium-activated protease calpain in the regulation of netrin-1/DCC-mediated cortical axon outgrowth and guidance

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During embryonic development, neurons extend axons towards their appropriate synaptic targets to establish functional neuronal circuits. The netrin family of guidance cues is vital for proper axon guidance. In particular, netrin-1 mediates its attractive function through the receptor deleted in colorectal cancer (DCC), which recruits proteins to mediate axon outgrowth and guidance. DCC is highly phosphorylated on Ser and Thr residues but its molecular significance remain elusive. Here, by using phosphoproteomic analysis, we identified T1210 in the cytoplasmic tail of DCC as a phosphorylation site important for the regulation of DCC proteolysis. Interestingly, the endogenous calpain inhibitor, calpastatin, was able to partially inhibit proteolysis of the mutant DCC-T1210V and to reduce the presence of DCC intracellular (ICD) fragments in HEK293 cells. In addition, the calcium-activated cysteine protease calpain was able to cleave DCC in vitro. We demonstrate that netrin-1 activates calpain in cortical neurons in a ERK1/2-dependent manner whereas cortical neurons expressing calpastatin display longer neurites. Finally, we show that netrin-1-mediated Erk1/2 activation was abolished in calpain-1/2-deficient neurons dissociated from Nestin-Cre; capns1 flox/flox embryos compared to control neurons. Altogether, we propose a novel model of DCC regulation whereby netrin-1/DCC-mediated axon outgrowth and guidance is regulated by calpain and that pT1210 protects DCC from proteolysis to maintain an intact DCC molecule at the cell surface of growth cones.

3-A -18 AMIGO-1 regulates the development of the olfactory sensory map

Reesha Raja[1], Alina Phen[1], Emilie Dumontier[1], Jean-François Cloutier[1]
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Perception of environmental signals relies on the precise establishment of neural maps, topographically connecting primary sensory and second order neurons. In the olfactory system, olfactory sensory neuron (OSN) axons rely on axon guidance and cell adhesion molecules (CAMs) to find their appropriate targets. OSNs expressing the same olfactory receptor (OR) innervate stereotypically-located glomeruli in the olfactory bulb (OB). Several guidance molecules help segregate axons into general regions of the OB, but the mechanisms governing axon coalescence into specific glomeruli are not fully understood. Differential expression of CAMs on axons is proposed to direct local axonal sorting, but considering the complexity of organizing OSN axons expressing over 1000 different ORs, it is likely that additional mechanisms are necessary for axonal sorting into individual glomeruli. We have identified a member of the 'amphoterin-induced gene and ORF' (AMIGO) family of transmembrane proteins as a regulator of glomerular formation. We show that AMIGO1 expression is restricted to ventrolateral zones of the olfactory epithelium, and AMIGO1-expressing OSNs project axons to the ventral OB. AMIGO1 ablation in mice causes a reduction in the number of neurons expressing the OR MOR28 leading to smaller MOR28 glomeruli, but does not affect the targeting of AMIGO1-negative MOR174-9-positive axons to the dorsal OB. These findings identify AMIGO1 as a regulator of olfactory map formation in mouse and suggest that AMIGO1 may regulate targeting of additional axonal populations during development.

3-A -19 Disruption of CREB-dependent transcription alters brain structural volume covariance

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The CREB protein is a transcription factor implicated in a variety of cellular processes. Previously, we found broad volume changes in CREB alpha/delta knockout mice ("CREB KO"). Here, we sought to explore whether loss of CREB results in altered structural covariance (covariance between region volumes, measured over a population, linked to structural and functional connectivity). Using MRI data

of wildtype (N=81) and CREB KO mice (N=68), the volumes of 62 structures were found. We looked for genotype-attributed changes in structural covariance between all pairs of region volumes. We found that 6 pairs of structures showed significantly different volume-genotype interactions (FDR $q < 0.05$) after accounting for multiple comparisons: 1) globus pallidus-arbor vita, 2) optic tract (OT)-fornix, 3) OT-habenular commissure, 4) cuneate nucleus-hypothalamus, 5) OT-stria medullaris, and 6) OT-third ventricle. Covariance magnitude was higher between all 6 pairs of regions in the CREB KO mice compared to controls; in CREB loss, these regions couple together more strongly in volume. Previous studies have shown that CREB is required for spatial memory and maternal nurturing, and also modulates response to reward. Given alterations in volume covariance involving the hypothalamus and habenula (neuroendocrine and reward systems), fornix (memory), arbor vita, globus pallidus (motor), and optic tract (visual), anatomical covariance changes due to CREB loss might reflect functional deficits in relation to reward, and also alterations in connectivity with memory, motor, and visual domains.

3-A -20 TrpV1 mediates axon degeneration in development

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Neurodegeneration has an essential role in refining the developing nervous system, but the destructive molecular pathways that normally remove an axon during development can be aberrantly reactivated during neurodegenerative disease. Sensory neurons expressing the TrkA neurotrophin receptor are supported by NGF, and local loss of NGF leads to degeneration of deprived axons. Here, we report that NGF withdrawal activates calcium influx before neurite degeneration, and that chelation of calcium robustly rescues loss of cytoskeletal and membrane integrity during NGF deprivation. Pharmacological inhibitors of calcium channels, including TrpV1 inhibitor capsazepine, rescue axons from degeneration. TrpV1 inhibition rescues NGF deprivation-induced mitochondrial fragmentation and loss of potential. NGF withdrawal induces oxidative stress, and TrpV1 inhibition rescues axons from reactive oxygen-induced calcium influx and degeneration. Understanding the molecular events upstream of neurotoxic calcium stress may provide therapeutic opportunities when these pathways are misregulated in disease.

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

3-B -21 Calcium-stimulated signaling pathway via adneylyl cyclase subtype 1 contreibutes to postsynaptic LTP in the insular cortex of adult mice

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Long-term potentiation (LTP) of synaptic transmission in the adult mouse insular cortex (IC) is a key model for cortical plasticity. The IC is widely believed to be an important brain structure involved in pain perception and memory processes. Adenylyl cyclases (ACs) are known about critical enzyme for LTP in the central nervous system (CNS). However, little is known whether ACs is required for LTP in the IC. In this study, using a whole-cell patch clamp method, we investigate the mechanism of postsynaptic form of LTP (post-LTP) in the IC, and examined whether post-LTP in the IC requires activations of ACs. Pairing stimulation induced post-LTP in layer II/III pyramidal neurons under the voltage-clamp mode. Induction of post-LTP in the IC required calcium-stimulate signaling pathway via N-methyl-D-aspartate receptors (NMDARs). AC subtype 1 (AC1) knockout mice, but not AC8, did not show post-LTP in the IC. NB001, a selective AC1 inhibitor, also blocked insular post-LTP. Furthermore, we found that protein kainase A (PKA) was also involved in the induction mechanism of post-LTP in the IC. Protein kinase M zeta (PKMæ)

was critical for the maintenance of post-LTP in the IC. Our results suggest that the mechanism of post-LTP in the IC may help to prevent or treat neuropathic pain.

3-B -22 Phosphoinositol hydrolysis regulates cation channel function in Aplysia neuroendocrine cells
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Reproduction in the marine snail, Aplysia, is initiated when the neuroendocrine bag cell neurons undergo a prolonged period of enhanced excitability and secretion, known as the afterdischarge. A voltage-gated, non-selective cation channel, similar to canonical transient receptor potential (TRP) channels, provides the depolarizing drive for the afterdischarge. Following an initiating cholinergic signal, phospholipase C (PLC) is activated during the afterdischarge, hydrolyzing phosphatidylinositol-4,5-bisphosphate (PIP2) into diacylglycerol (DAG), a protein kinase C (PKC) activator, and inositol trisphosphate (IP3), a mobilizer of internal Ca2+. Pretreatment of bag cell neurons with a PLC activator, m-3M3FBS, left-shifted cation channel voltage-dependence in excised, inside-out patches; this was also the same for a DAG analogue, OAG, but not to the same degree. Triggering PKC with a phorbol ester had no effect on voltage-dependence, consistent with DAG directly interacting with the cation channel, analogous to TRPC channels. Applying m-3M3FBS to untreated, excised patches increased channel open probability, suggesting PLC may be closely-associated with the channel. Intriguingly, PIP2 pretreatment modestly left-shifted voltage-dependence, and PIP2 application to patches increased channel activity. Regulation of cation channel activity by the products of PIP2 hydrolysis was more potent than by PIP2 itself, and appears to involve lipid-protein interactions. This may temporally control afterdischarge duration and ultimately reproductive behaviour in Aplysia.

3-B -23 Cav3.1-mediated calcium entry triggers signaling cascade for CREB activation
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Calmodulin (CaM) is an important signalling molecule that regulates a vast array of second messenger cascades that can also lead to gene transcription. Low voltage-activated calcium channels of the Cav3 family have the important role of mediating low threshold calcium influx, but were not believed to interact with CaM. We find a constitutive association between CaM and the Cav3.1 channel at rest that is lost through an activity- and Cav3.1 calcium-dependent CaM dissociation. Moreover, Cav3 calcium influx activates αCaMKII in the cytoplasm and phosphorylation of CREB in tsA-201 cells, cultured hippocampal cells and cerebellar Purkinje cells. Recent work has revealed a Cav3.1 channel-dependent LTP of cerebellar parallel fiber input to Purkinje cells. Delivering a theta burst pattern of optogenetic stimuli to parvalbumin-ChR2 expressing Purkinje cells in vitro is sufficient to evoke a mibefradil-sensitive Cav3.1-mediated LTP of a simulated postsynaptic EPSP in Purkinje cells. LTP of the EPSP was reduced by the CaMKII blocker AIP, and poststimulus immunolabeling revealed phosphorylation of CaMKII and CREB in lobule 9 Purkinje cells. Our findings thus establish that T-type channel calcium influx invokes a novel dynamic interaction between CaM and Cav3.1 channels and triggers a signaling cascade directly relevant to postsynaptic LTP of the parallel fiber EPSP in Purkinje cells. Supported by CIHR OOGPs (RWT, GWZ, PKS), AIHS and QEII Studentships (APR), and University Calgary Eyes High and AIHS Postdoctoral Fellowships (GS).

3-B -24 Synaptic vesicle recycling defects in de novo mutations of dynamin 1
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The large neuron-specific GTPase, dynamin 1, plays an essential role in synaptic vesicle recycling. During clathrin-mediated endocytosis (CME), dynamin 1 induces fission of the membrane through GTP hydrolysis at the vesicle neck. Dynamin 1 also plays a role in the formation of vesicles from bulk endosomes, following activity-dependent bulk endocytosis (ADBE). We have identified de novo dynamin 1 mutations in patients with either epilepsy, developmental delay, or comorbid for both of these disorders. We hypothesized that these de novo mutations in dynamin 1 may alter synaptic vesicle endocytosis. We evaluated the impact of these mutations on the 3-D structure of dynamin 1. All mutations identified were predicted to be deleterious for dynamin 1 function. To determine whether these mutations impacted its synaptic role, we used the genetically encoded reporters, synaptophysin-pHluorin (sypHy) and vesicle associated membrane protein 4-pHluorin (VAMP4-pHluorin) to visualize both CME and ADBE in embryonic mouse hippocampal neurons. Intriguingly, we identified that specific dynamin 1 mutants had different effects on both CME and ADBE. These defects in synaptic vesicle (SV) endocytosis may therefore underlie some of the symptoms displayed by these patients. They also suggest that dysfunctional SV endocytosis may be a common underlying event across different neurodevelopmental disorders, providing a novel avenue for future treatment strategies. Finally, these studies provide further insight regarding the potentially divergent molecular role(s) of dynamin 1 in presynaptic function.

3-B -25 GCaMP imaging reveals that combined changes in axonal excitability and intracellular chloride are necessary to permit GABA-evoked spiking in the central axon terminals of primary afferent neurons

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Under normal conditions, spikes in primary afferent neurons originate in peripheral axon terminals and propagate to the CNS. However, GABA acting on central axon terminals causes primary afferent depolarization (PAD), which, while normally inhibitory, can lead to spikes that propagate antidromically. From somatic recordings, PAD-evoked spiking has been shown to require both a depolarizing shift in EGABA and reduced K+ conductance. This combination of effects can arise in damaged peripheral nerves via enhanced function of the Na-K-Cl cotransporter, NKCC1, and by downregulation of Kv1-type potassium channels, respectively. However, it remains unclear if these requirements are met at central axon terminals. Using GCaMP6f transgenic mice, action potential evoked calcium transients were measured in somata in the dorsal root ganglion with high spatial and temporal resolution, allowing us to view antidromically propagating spikes evoked by application of GABA to axon terminals in the spinal cord. Aldosterone, an NKCC1 enhancer, was found to depolarize EGABA, and only when aldosterone was simultaneously applied with a Kv1-type channel blocker, 4-AP, could GABA initiate antidromically propagating spikes from central axon terminals. These data confirm that enhanced chloride loading via NKCC1 and enhanced excitability caused by reduced Kv1-type conductance are necessary for PAD-evoked spike initiation at central axon terminals. Consequently, these GABA-evoked spikes can propagate antidromically to cause neurogenic inflammation via the peripheral release of inflammatory mediators.

3-B -26 Hydrogen peroxide gates a cation channel in Aplysia neuroendocrine cells

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Non-selective cation channels pass Na+, K+, and sometimes Ca2+ to elicit plateau potentials and persistent spiking in neurons responsible for learning, sensory input, motor output, or neuroendocrine function. In the bag cell neurons of the marine snail, Aplysia, opening of Ca2+-permeable, Ca2+-activated, voltage-dependent cation channel provokes a prolonged afterdischarge and the release of hormones to initiate reproduction. The afterdischarge is associated with the production of reactive oxygen species; as such, we tested the effects of hydrogen peroxide (H2O2). Under whole-cell voltage-clamp, H2O2 elicited a voltage-dependent inward current in cultured bag cell neurons, with an EC50 of 300 µM. Compared to normal saline, the amplitude of the current was significantly smaller in Ca2+-free, Na+-free, or Ca2+/ Na+-free extracellular saline, while the reversal potential was significantly left-shifted, consistent with a non-selective cation channel. Application of 9-phenanthrol, a cation channel blocker, increased the %-recovery of the H2O2-evoked current. Ca2+-influx, mediated by a 1-Hz, 1-min train-stimulus of depolarizing steps significantly depressed the recovery of the H2O2-evoked current. A similar impact on recovery was observed with an intracellular perfusion of adenosine diphosphate ribose (ADPR), followed by a 5-Hz, 10-sec stimulation. This suggests that there is a synergistic relationship between H2O2 and ADPR, which results in the recruitment and activation of Ca2+-activated, voltage-gated cation channel to maintain the afterdischarge.

3-B -27 Visualization of lncRNAs, ion channels, and GPCR expression, within morphological context in the central and peripheral nervous systems

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The nervous system consists of numerous specialized cell types that remain to fully cataloged and characterized at the molecular level. Due to the high degree of structural and functional heterogeneity and the intricate spatial organization of these cells, it is of special importance to analyze gene expression in the presence of full morphological and spatial contexts. Due to the lack of specific antibody reagents, especially for lncRNAs, G-protein coupled receptors (GPCRs), and ion channels, mapping of specific transcripts by in-situ hybridization offers an excellent alternative approach. The RNAscope® assay provides a powerful method to detect gene expression within the spatial and morphological tissue context. The robust signal-to-noise technology allows for detection of gene transcripts at single molecule level with single-cell resolution analysis and can further expand our understanding of gene expression in complex tissues environment. In this study, by applying multiplex RNAscope assay, we demonstrate specific detection of (1) two lncRNAs, Neat1 and Malat1, in the mouse hippocampus, (2) four types of GPCRs in hippocampal, striatal and cortical mouse brain areas: Drd1 and Drd2, Cnr1, and Chrm3, (3) two ion channels ASIC1 and KCNJ3 in mouse brain hippocampus, and (4) multiple target co-expression patterns with desired cell type markers for the detection of neurons, microglia, and astrocytes. The RNAscope® technology allows visualizing tissue-restricted expression of any transcript with distinct subcellular structures and regulated expression patterns.

3-B -28 Action potential counting at giant mossy fiber synapses gates information transfer in the hippocampus

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Neurons encode information in the number and frequency of action potentials they discharge. Calcium-induced neurotransmitter release occurs in presynaptic terminals as a result of action potential firing. How presynaptic terminals decode the frequency and the number of action potentials in incoming bursts through specialized calcium dynamics remains unknown. To investigate how presynaptic

terminals translate bursts of APs to neurotransmitter release, we combined electrophysiology with random-access two-photon presynaptic calcium imaging in hippocampal mossy fiber terminals. We found that the number of action potential in a burst was encoded in the spatial homogenization of calcium microdomains, while the average frequency of APs controlled the peak calcium amplitude. AP transmission to the CA3 pyramidal cell was dependent on the number of action potential in the burst, but was independent of the AP burst average frequency. Our results indicate that presynaptic mossy fiber terminals favor a counting logic over rate or temporal coding. Therefore, mossy fiber terminals count the number of action potentials in bursts through the spatial homogenization of calcium microdomains to gate action potentials propagation to CA3 pyramidal cells.

3-B -29 Employing a fast, membrane-targeted GCaMP variant to study the spatial distribution of voltage-gated calcium channels at presynaptic specializations

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Calcium signals in neurons are highly compartmentalized. Spatially restricted, large amplitude calcium transients likely exist at presynaptic specializations of neurons releasing neurotransmitters such as glutamate, a process that requires calcium binding to the low-affinity synaptotagmin-I/II. Studies using BAPTA-based indicators to measure calcium in the bulk cytosol have provided evidence for spatially restricted signalling in preparations such as neuromuscular junctions, but yielded little information about the spatial distribution of presynaptic voltage-gated calcium channels. Genetically encoded calcium indicators (GECI), due to their ability to be targeted to subcellular compartments, are promising tools to probe presynaptic calcium compartmentalization. Here we demonstrate that GCaMP6f/EF12_mCherry_tKRAS, a plasma membrane-targeted GECI with low calcium affinity and fast kinetics, allows for ratiometric quantification of calcium transients in axons of cultured hippocampal neurons in response to isolated action potentials. Evoked calcium transients are largely confined to presynaptic specializations and decay exponentially within a few micrometers. Axonal shaft regions at some distance from synapses often show detectable, but much smaller calcium transients that vary strongly in amplitude between individual neurons. Our results demonstrate that newest generation GECIs are outstanding tools to measure calcium transients in small subcellular domains and indicate that voltage-gated calcium channels in axons are highly localized to presynaptic specializations.

3-B -30 A novel computational model underlying the spiking dynamics of a subfornical organ neuron

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The subfornical organ (SFO) plays an important role in sensing blood-borne signals regarding important autonomic functions from the periphery and projecting them across the blood-brain barrier (BBB). Previous findings from in vitro studies have established that SFO neurons exhibit an immense heterogeneity in their spiking behaviour, expression of ionic currents, and responses to peptidergic signals, but the detailed mechanisms underlying these differences are less understood due to the limitations of patch-clamp techniques. Here we present a novel computational model of a subfornical organ neuron as an approach to understanding the mechanisms behind this heterogeneity. Precise current-voltage properties of our Izhikevich-style model suggests that a combination of membrane noise and subthreshold oscillations are responsible for the irregular bistability that is characteristic of SFO neurons. Reproducibility of SFO-specific spiking patterns was established through statistical analysis of spike-train variability (CV) in both the model's simulations and in vitro recordings of SFO neurons. This technique allows us to classify individual neurons as exhibiting one of two prominent behaviours seen in

SFO neurons, either bursting (CV > 1) or tonic (CV < 1) firing. This model has future application in exploring the ionic mechanisms underlying the various SFO spiking profiles as well as predicting the behaviour of these neurons in response to various peptidergic signals.

3-B -31 Ionotropic and metabotropic kainate receptor signalling regulates KCC2 and synaptic inhibition

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The potassium-chloride cotransporter 2 (KCC2) plays a critical role in inhibitory neurotransmission through its ability to maintain low intracellular chloride levels in mature neurons. KCC2 has also recently been found to interact with proteins involved in excitatory neurotransmission, including the kainate receptor (KAR) subunit GluK2. However, it is unknown whether the activity of kainate receptors can directly influence KCC2 function. In this study we hypothesized that the activation of GluK2-containing kainate receptors would increase KCC2's ability to extrude chloride from the neuron. We tested this hypothesis by performing slice electrophysiology experiments in the CA3 region of the hippocampus. Activation of KARs with kainite produced a significant hyperpolarization in EGABA and a dramatic increase in the driving force for Cl- through the GABAA receptor, and thus an increase in GABAergic current amplitudes. Selective activation of metabotropic signalling of KARs, produced an even larger hyperpolarization of EGABA that persisted after washout. Selection activation of ionotropic signalling of KARs with the addition of the G-protein inhibitors n-ethymaleimide (NEM) or GDP-βS also produced a significant hyperpolarization in EGABA, which returned to baseline after washout. This effect is not present in the GluK2/3 knockout. These results suggest that the two KAR signalling pathways exert independent effects on KCC2. Our findings demonstrate that activation of the kainate receptor regulates KCC2 function, revealing a novel mechanism for excitatory: inhibitory balance.

3-B -32 Use of optogenetics to trigger and characterize somatodendritic dopamine release in the mouse mesencephalon

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Dopamine (DA) release in the brain occurs from axon terminals thought a classical exocytotic mechanism. However, DA can also be released from the somatodendritic (STD) compartment of DA neurons. The molecular mechanisms of STD DA release are unclear. STD DA release has been previously studied in mouse brain sections by combining extracellular field stimulation with cyclic voltammetry or with patch-clamp recordings of D2-mediated currents. An important limitation of this approach is that extracellular stimulation non-selectively depolarizes DA neurons as well as local terminals and cell bodies of GABA and glutamate neurons, in addition to axon terminals containing 5-HT, which can complicate analysis of cyclic voltammetry recordings. Here we further explored this unconventional form of transmitter release in mouse brain slices by combining optogenetics to selectively activate DA neuron cell bodies and cyclic voltammetry. For this purpose, a mouse line expressing the light-activated channelrhodopsin (ChR2) was crossed with a DA-specific Cre driver mouse line (Ires-Dat-Cre) to selectively express ChR2 in DA neurons. We find that train pulses of blue light can effectively trigger an electrochemical response of small amplitude, that can be increased in magnitude by blocking the membrane DA transporter (DAT) and the D2 autoreceptor. The capacity of this releasable DA pool appears to be small, as repeated train pulses with an interval of 5-10 min lead to a large decrement of the response. We are presently exploring strategies to increase the size of the releasable STD DA pools.

3-B -33 State-Dependent Entrainment of Cortical Oscillatory Activity

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Numerous studies have shown that that periodic stimulation, such as Repetitive Transcranial Magnetic Stimulation (rTMS) and Transcranial Alternating Direct Current Stimulation (TACS), can be used to engage cortical rhythms. Such findings have raised the fascinating prospect of manipulating rhythmic brain activity in a controlled manner, engaging neural circuits at a functional level to manipulate cognition and treat brain disorders. But the brain is not a passive receiver: brain stimulation, either intracranial or non-invasive, has a variable impact on brain dynamics whether stimulated neurons are recruited in a task or not. Indeed, the effects of stimulation on neural populations is regulated by neural excitability, implying that control over cortical oscillations is state-dependent. We here used computational approach to study the role of ongoing state on the entrainment of cortical neurons. We examined whether state-dependent changes in thalamo-cortical dynamics could implement a gain control mechanism regulating cortical susceptibility to stimulation. First, our analysis shows that increased drive to the thalamus is sufficient to trigger the suppression of resting state cortical oscillations. We found that the resulting increase in irregular fluctuations during task states enables a greater susceptibility of cortical neurons to entrainment, through a mechanism akin to stochastic resonance. Taken together, our results provide new insights about the state-dependent interaction between rhythmic stimulation and cortical activity.

3-B -34 NOREPINEPHRINE AND L-LACTATE MODULATION OF NEURAL NETWORK ACTIVITY IN NEWBORN RAT LOCUS CERULEUS SLICES

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In cultured locus ceruleus (LC) slices, photoactivated astrocytic lactate release excites adjacent neurons via a yet unknown receptor (Tang et al [2014] Nat Commun 5:3284). Here, we studied this neuron-glia signaling further with bath-application of lactate and norepinephrine (NE) receptor (ant)agonists in acute 0-4 days-old rat brainstem slices. A rhythmic field potential (rFP, rate 1-3 Hz) in the LC and Fluo-4-AM-imaged cytosolic calcium (Cai) dynamics were simultaneously monitored in tyrosine hydroxylase-positive LC neurons and S100β-positive astrocytes in the LC and a <500 µm perimeter around the LC. NE (25 µM) caused a Cai rise in pericoerulear astrocytes that propagated to the LC whereas LC neurons showed a Cai decrease concomitant with slowing of rFP rate. The α1 NE receptor agonist phenylephrine (25 µM) mimicked the NE-evoked concentric astrocytic Cai wave, but raised neuronal Cai and accelerated rFP rate. L-lactate (2 mM) increased rFP rate and Cai in a subpopulation of LC neurons and these effects persisted in presence of the monocarboxylate transporter blocker 4-CIN (250 µM). Our results indicate that neurons within the acutely isolated LC express a novel lactate receptor. We hypothesize that a NE induced Cai increase in astrocytes causes α1 receptor-mediated lactate release that excites LC neurons to counteract the concomitant α2 receptor-mediated depression of their rhythmic discharge. This supports the view that lactate acts as a gliotransmitter to finetune LC activity and thus NE release in brain regions innervated by the LC. Supported by NSERC, AIHS, CFI.

3-B -35 Regulation of Calcium Entry in Microglia by Nitric Oxide

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Background - Nitric oxide (NO) regulates microglia activity which is associated with calcium (Ca^2) entry, primarily via store operated Ca^2 (SOC) channels and transient receptor potential vanilloid (TRPV) channels. New data from our laboratory showed that NO inhibits SOC conductance by S-nitrosylation of STIM1. This study set forth to examine whether NO regulates Ca^2 entry in microglia. Methods - Ca^2 imaging, patch-clamp recording, immunoblot and immunocytochemistry were used to examine effects of the NO-donor SNAP (250µM), on SOC and TRPV channels, as well as Ca^2 entry. Experiments were conducted on BV2 microglia and microglia isolated from wild type (WT) and iNOS-/- mice. Results - Bath application of SNAP induced a rapid decrease of an existing non-selective cation conductance and basal intracellular Ca^2. This short-lasting response was followed by a long-lasting enhancement in conductance and Ca^2 entry. The biphasic actions of SNAP were more effective in iNOS-/- microglia than in WT microglia. The SNAP-inhibition became smaller in the presence of a SOC channel inhibitor, while the SNAP-enhancement was reduced by a TRPV inhibitor. Immunoblotting and immunocytochemical assays revealed a higher level of TRPV2 protein in the plasma membrane of SNAP-treated microglia. Greater phagocytosis of IgG beads occurred in SNAP-treated microglia. Conclusion - Available data suggests that NO regulates Ca^2 entry in microglia by inhibiting SOC channels, but enhancing translocation of TRPV2 channels to the plasma membrane.

3-B -36 Regulation of oligodendroglial mitochondria by netrin-1

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The form and function of axonal mitochondria have been well described; however, the presence of mitochondria in the oligodendroglial myelin sheath has only recently been reported (Rinholm et al. 2016). Mitochondria produce ATP and carbon chain backbones that are essential for the synthesis of lipids and myelin but little is known about how mitochondrial function is regulated in oligodendrocytes. Here we show that mitochondrial dynamics in oligodendrocytes are regulated by the secreted extracellular protein netrin-1. Netrin-1 and netrin receptors are enriched at oligodendroglial paranodal junction in the CNS and loss of netrin-1 or DCC function destabilizes myelin (Jarjour et al. 2008; Bull et al. 2014). We show that bath application of netrin-1 rapidly induces hyper-elongation of mitochondria while inhibition of a downstream signaling pathway results in severe mitochondrial fragmentation. Longer-term exposure to netrin-1 results in a decrease in OXPHOS and an increase in glycolysis in oligodendrocytes. Furthermore, we show that mitochondria are recruited to, and remain aggregated at, a local source of netrin-1. Using super-resolution structured illumination microscopy (SIM), we resolve mitochondria and a mitochondrial docking protein at the surface of netrin-1 coated beads. These findings demonstrate the regulation of mitochondrial fusion, fission, migration; and cellular respiration in oligodendrocytes by netrin-1. Our ongoing studies are investigating the specific signalling pathway downstream of netrin-1 regulation of mitochondrial dynamics in oligodendrocytes.

3-B -37 Changes in extracellular Ca2+ concentration trigger sustained firing in a precise axonal compartment of large primary afferents through Nav1.6 channels

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Large diameter primary afferents have rapid subthreshold membrane oscillations (SMO) that increase in amplitude and lead to ectopic firing which has been linked to neuropathic pain after nerve injury. These discharges could represent a target for therapy, but the site at which they are generated remains unclear. Similar changes in intrinsic electrical properties are observed in mesencephalic trigeminal (NVmes) cells innervating muscle spindle afferents of the jaw closing muscle in a chronic muscular pain

model. The SMO in these neurons rely on a persistent sodium current (INaP), which has been shown to be inversely modulated by extracellular calcium concentration ([Ca2+]e). Interestingly, Nav1.6 channels, which are known to support INaP, have been reported to underly SMO in NVmes. Thus, to localize the sodium channels underlying these SMO, we used whole-cell patch-clamp recordings, confocal imaging and immunohistochemistry methods on mice or rat brain slices. We found that restricted [Ca2+]e decreases produced by local BAPTA applications near the soma have no effect on either SMO or firing, whereas applications along the axon promoted SMO and sustained firing. Interestingly, this effect was maximal in a precise axonal compartment at a slight distance from the axon hillock where immunostaining confirmed an enrichment of Nav1.6. Furthermore, 4,9-anhydroTTX, a selective blocker of Nav1.6 channels, abolished SMO and firing induced by BAPTA. These data suggest that a specific axonal subregion may play an important role in the development of ectopic activities present in pain.

3-B -38 Effects of high frequency electric field stimulation on neuronal function

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Spinal cord stimulation (SCS) is a neuromodulation technique used to reduce chronic pain. Conventional SCS involves electrical pulses delivered at around 100 Hz. This low-frequency stimulation reduces pain by activating dorsal column fibers that engage inhibitory mechanisms at the spinal level, but also causes a tingling sensation (paresthesia) that some patients find uncomfortable. Newer forms of SCS involve electrical pulses delivered at frequencies between 1 and 10 kHz. High-frequency SCS may yield comparable pain relief without causing paresthesia, but its mechanism remains unclear. One study has suggested that high-frequency electric field stimulation (hfEFS) induces neuronal hyperpolarization, which could help alleviate pain by reducing the number of action potentials produced by pain-sensing neurons. To investigate hfEFS-induced hyperpolarization, we applied hfEFS to cultured pyramidal neurons while monitoring their membrane potential using whole cell patch clamp and voltage-sensitive dye (VSD) imaging. The frequency and amplitude of hfEFS were varied between 1-10 kHz and 0.5-5 mA. By repeating VSD imaging on the same neuron before, during and after patching, we found that hfEFS-induced hyperpolarization varied based on the recording conditions. hfEFS-induced hyperpolarization was accompanied by an increase in rheobase, indicating that the hyperpolarization was not a recording artifact. The basis for this phenomenon remains unclear. Funded by Boston Scientific Corporation.

3-B -39 Nicotinic Acetylcholine Receptor Signaling in Principal Neurons of the Developing Hippocampus Formation

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The excitatory circuit in the hippocampus formation (HF) is composed of glutamatergic principal neurons of the cornu ammonis (CA) area 1, CA3, dentate gyrus (DG), subiculum (SUB) and entorhinal cortex (EC). The normal development and function of this neuronal network depends on the ability of nicotinic acetylcholine receptors (nAChRs) to mediate afferent signaling by acetylcholine (ACh). While the α4β2* nAChR subtype constitutes a major class of nAChRs in the HF, its ability to mediate nicotinic signaling in glutamatergic principal neurons of the HF is not well understood. We first sought to determine whether functional α4β2* nAChRs are present on principal neurons located within the CA1, CA3, DG, SUB and EC layer VI of male CD1 strain mice during early postnatal development by measuring their whole-cell electrophysiological responses to ACh within acute brain slices. We found that α4β2* nAChRs elicit postsynaptic inward currents and facilitate neuronal excitation from rest in principal neurons of all regions investigated, and that these responses are greatest in the SUB and EC layer VI. Interestingly, the

response to ACh in active neurons that were previously induced to fire action potentials was similar across all regions and this similarity resulted from modulation by the calcium-activated potassium channels of the small conductance type. Since this activity of α4β2* nAChRs in HF principal neurons occurs during a developmental period of synaptic integration, these results suggest a role for α4β2* nAChRs in the formation and maturation of synchronous hippocampus networks.

3-B -40 Properties of electrical transmission promote synchronization of Aplysia neuroendocrine cells

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Gap junctions form the basis of electrical synapses and promote synchronized spiking by allowing for the rapid transfer of current between neurons. In the marine snail, Aplysia calfornica, two clusters of electrically coupled neuroendocrine bag cell neurons coordinate a lengthy synchronous burst, known as the afterdischarge, to secrete egg-laying hormone and initiate ovulation. We tested the efficiency of electrical transmission between pairs of coupled bag cell neurons in culture under whole-cell voltage- or current-clamp. Junctional current was linear from -90 to 0 mV, but exhibited inward rectification from 0 to +60 mV. When measured at -60 mV, presynaptic input resistance dropped from nearly 200 to 100 MΩ with increasing hyperpolarization (-50 to -250 pA). The pre- to postsynaptic coupling coefficient, on the other hand, remained unchanged at about 0.5 through the same series of negative current steps. Presynaptic action potentials transferred much less than 50%, evoking postsynaptic electrotonic potentials of close to 10 mV with a 15-ms peak-to-peak latency. Thus, steady-state hyperpolarization between neurons transfers very efficiently, despite a drop in presynaptic input resistance at more negative voltages. However, depolarizing transfer is far less efficient, which may be attributed to both inward rectification at positive voltages and low-pass filtering properties of the gap junction. For the afterdischarge, gap junctions may promote synchronization more than recruitment, which is consistent with most neurons in the cluster processing their own burst mechanism.

3-B -41 Optical imaging of netrin-1 exocytic events in cultured hippocampal neurons

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Netrins are a family of secreted proteins that were first identified as guidance cues, directing cell and axon migration during neural development. Netrin-1 and its receptor DCC are widely expressed by neurons during synapse formation and in the mature brain. The mechanisms underlying the exocytosis of netrin-1 and its spatial dynamics after its secretion have not been studied. To investigate netrin exocytosis, we transfected cultured rat hippocampal neurons with super-ecliptic phluorin (SEP-netrin-1) and performed wide-field microscopy. We observed that upon plasma membrane fusion, single vesicles containing SEP-netrin could be detected on dendrites. These events occur at synaptic and extrasynaptic sites, and multiple release events can occur at the same site. Furthermore, secreted SEP-netrin was stable at the release site for a prolonged period (>100 sec), suggesting that netrin-1 accumulates on extracellular membranes at the periphery of synaptic sites. Our findings also suggest that the frequency of netrin-1 exocytosis is activity-dependent. To examine the spatial dynamics of secreted netrin-1, we tagged SEP-netrin-1 with single quantum dots and used single particle tracking on neurons expressing post-synaptic marker Homer-DsRed. Our findings indicate that netrin-1 exhibits two main modes of diffusion, one that is confined to synaptic areas and one that is Brownian-like at non-synaptic sites. Our experiments provide insight into the molecular mechanisms underlying the contribution of netrin to the development of synapses and neural circuit formation.

3-B -42 VIP interneuron diversity in the mouse hippocampus

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Vasoactive intestinal peptide-expressing (VIP+) interneurons occupy a distinct niche in interneuron population as many of them specialize in innervating GABAergic cells and providing network disinhibition. In the CA1 hippocampus, two major types of VIP+ interneurons were described so far: basket cells that innervate pyramidal cells (VIP-BCs) and the interneuron-selective (VIP-IS) cells that target interneurons. To examine molecular diversity of hippocampal VIP+ neuronal population, we examined expression of neurochemical markers by VIP+ cells in two most commonly used mouse models: VIP-eGFP (CD1 background, GENSAT) and VIPCre-tdTomato (C57Bl6 background, The Jackson Lab). Our data revealed at least 4 different subtypes of VIP+ cells within the CA1 oriens/alveus (O/A) and other hippocampal regions that could be distinguished by differential expression of the cholecystokinin, calbindin, calretinin and the muscarinic receptor. VIP+ O/A cells were negative for nitric oxide synthase and somatostatin. The neurochemical diversity of VIP+ O/A cells was further confirmed by distinct morphological and electrophysiological properties, revealing specific features of VIP-BCs, VIP-IS3 and of a novel long-range VIP+ neuron that innervates CA1 and subiculum. The proportion of different cell types varied between the two mouse models, highlighting the mouse-specific VIP+ cell types. Together, our data reveals the heterogeneity of VIP+ cell population in the CA1 hippocampus and points to their cell-specific function within hippocampal circuitry.

3-B -43 Neural populations with feedforward inhibition and background conductance noise operate as smart filters

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The prodigious capacity of our brain to process information relies on efficient neural coding strategies. Intrinsic neuronal properties and synaptic connectivity patterns are key determinants of how reliably information is transmitted. We show here through computer simulations of feed-forward networks of Morris-Lecar model neurons that feedforward inhibition (FFI) can filter shared synaptic input so as to maintain low-frequency (0-10 Hz) information while amplifying mid-frequency (10-1000 Hz) information. To further investigate the filtering characteristics of neural populations with FFI, we calculated the power spectral density (PSD) of spikes normalized to firing rate in response to shared synaptic input and with each neurons receiving independent conductance noise. Whereas the number of neurons affected the total power without affecting the shape of the PSD, varying the synaptic time constants affected the PSD shape; specifically, making the time constants for excitatory and inhibitory input more similar accentuated mid-range frequencies. Interestingly, we found that changing the delay between excitation and inhibition (from 3 to 8 ms) had negligible effects on PSD shape. In summary, we demonstrate that ensembles of neurons can implement smart filters using FFI coupled with background conductance noise. This can be used to enhance the reliable transmission of signals comprising a range of frequencies, and can do so under realistically noisy conditions. This work is funded by Fonds de recherché du Quebec - Sante (FRQS).

3-B -44 The X-linked disability gene, DHHC9, regulates neural circuit formation

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The family of DHHC proteins, which encode palmitoyl acyltransferase enzymes, have been implicated in a number of neurodegenerative and neurodevelopmental disorders. Loss-of-function mutations in DHHC9 have been identified in patients with X-linked intellectual disability, however its role in the development and function of neural circuits is still unknown. Here we demonstrate that DHHC9 is localized to neurons where it plays an important role in promoting and maintaining dendritic growth and arborisation, as well as modifying synapses. Our data suggests that this is palmitoylation dependent and is mediated through small GTPases, such as Ras. Together these results show that DHHC9 targets these small GTPases to the plasma membrane, leading to the regulation of neuronal growth and synaptic density.

3-B -45 A double dissociation of presynaptic NMDA receptor signalling in neocortex

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Presynaptic NMDA receptors (preNMDARs) have been found at specific central synapses, where they enhance vesicle release through unknown molecular mechanisms. Using quadruple whole-cell recordings of layer-5 pyramidal cells in acute visual cortex slices from P11-17 mice, we found that preNMDAR blockade with the GluN2B-specific blocker Ro25-6981 reduced neurotransmission during spontaneous release (~2.5Hz) but only down-regulated evoked release at frequencies above 8.5 Hz. We therefore hypothesized that preNMDARs regulate spontaneous and evoked release through divergent mechanisms. Knocking out Rab3-interacting molecule (RIM) 1αβ -- a presynaptic scaffolding and vesicle pre-priming protein -- caused a reduction in baseline release during evoked but not spontaneous neurotransmission. The reduction of evoked release by RIM1αβ KO occluded any further decrease by preNMDAR blockade. The effect of preNMDAR blockade on spontaneous release, however, remained intact in RIM1αβ KO mice. In contrast, slices incubated in SP600125 -- a blocker of the C-Jun N-terminal kinase 2 (JNK2) known to affect regulation of release probability -- were unaffected by preNMDAR blockade during spontaneous release, whereas evoked neurotransmission was reduced. We conclude that in layer-5 pyramidal cells, preNMDARs modulate evoked and spontaneous release through separate pathways: RIM1αβ is required to regulate evoked but not spontaneous release, whereas JNK2 signaling is needed for regulation of spontaneous but not evoked release.

3-B -46 Pre-gating conformational changes of AMPA receptors are modulated by the flip/flop alternative splicing cassette

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Upon ligand binding, AMPA-type ionotropic glutamate receptors (AMPARs) undergo conformational changes that coincide with activation and/or desensitization. Comparatively little is known about the conformational flexibility of the resting, pre-gating state of AMPARs. Here, we used a combination of atomic force microscopy and electrophysiology to demonstrate that halide ions alter the overall resting height of GluA2 AMPARs, a change that predicts the desensitization kinetics following L-glutamate application. GluA2i (flip) AMPARs were found to be highly sensitive to both anion-induced height changes and kinetic modulation whereas these effects were significantly attenuated in GluA2o (flop) AMPARs. Crystallographic analysis of bromide-bound GluA2 ligand-binding domain dimers identified a

critical residue within the alternately-spliced flip/flop cassette responsible for regulating the extent of anion modulation. Accordingly, we propose that anion-induced, isoform-specific conformational changes "prime" resting AMPARs to respond in a specific manner to agonists.

3-B -47 Sexually Dimorphic Modulatory Effect of Estradiol on GABA Transmission

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The oval bed nucleus of the stria-terminalis (ovBNST) is one of the most sexually dimorphic regions of the brain, containing androgen, estrogen and progestin receptors in both male and female rats. Using whole-cell patch-clamp electrophysiology we examined how estrogens modulate GABA mediated Inhibitory-post synaptic currents (IPSC) in the ovBNST in Long-Evans rats of both sexes. Here we report that in both male and female rat's estradiol acting on estrogen receptor alpha is a potent modulator of GABA IPSC's. However, in female rats that were either in diestrus, estrus or had their ovaries removed the magnitude of estradiol's effect on GABA IPSC's is reduced compared to males. Moreover, orchiectomy in males and ovariectomy in females appeared to have no effect on estradiol's ability to modulate GABA IPSC's in the ovBNST, suggesting a gonad independent hormone system in the ovBNST. Furthermore, we report that that endogenous production of estradiol appears to be required for a low-frequency activity induced long-term potentiation of GABA IPSC's in males. However, in female rats we observe that the same plasticity protocol can produce a different response and cause a long-term depression of these GABA IPSC's in a sub-population of neurons. These results suggest that GABA plasticity within the ovBNST is sexually dimorphic. We conclude that endogenously produced estrogens are potent modulators of GABAergic activity within the ovBNST of both sexes.

3-B -48 RAGE signalling mediates hippocampal dysfunction in a mouse model of diabetes

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A robust association between diabetes and nervous system abnormalities has been observed. Among these complications, changes in hippocampal synaptic plasticity and cognitive abnormalities have been reported in animal models of diabetes. Increased expression of the Receptor for Advanced Glycation End-products (RAGE) has been identified as a key step in developing nervous system complications, still the underlying mechanisms are poorly understood. Therefore, we hypothesized that activation of RAGE signalling in diabetes alters glutamate receptor function, leading to deficits in long-term potentiation (LTP) and cognitive decline. Our findings showed that high glucose led to a significant reduction in AMPA-evoked currents in cultured hippocampal neurons from wild type (WT) but not from RAGE-knockout (RAGE-KO) mice. Immunoblotting analysis revealed that high glucose induced an increase in RAGE and a decrease in GluR1 subunit of AMPA receptor in the WT group, while decrease in GluN1 subunit of NMDA receptor was observed in both WT and RAGE-KO samples. Field excitatory postsynaptic potentials were significantly decreased in brain slices from WT diabetic mice, but not RAGE-KO diabetic mice. The latter was accompanied by an increase in paired-pulse facilitation ratio in both groups. Thus, we identified RAGE-dependent and -independent hippocampal abnormalities in diabetes. Our findings suggest that alterations in AMPA receptor function, GluR1 subunit expression, and LTP expression are mediated by RAGE expression and signaling in models of diabetes.

3-B -49 Sequential spatiotemporal activity in primary visual cortex reflects locomotion state.

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Temporal patterns of activity are prevalent in the cerebral cortex in vitro and in vivo yet their function is poorly understood. Here we use in vivo two-photon calcium imaging from awake behaving mice and document the existence of repeated patterns of activity in visual cortex during locomotion and rest. Surprisingly, different spatiotemporal patterns are specifically associated with the locomotion state of the animal, even in the dark. These patterns engage both excitatory and inhibitory neurons in a sequential fashion. We conclude that V1 acts as a multimodal cortical area and encodes the locomotion state of the animal by using spatiotemporal activity patterns. We propose that these patterns reflect a corollary discharge signal from cortical motor areas, and are shaped by the architecture of local inhibitory microcircuits.

3-B -50 Determinants of spinal hyperexcitability in a human ex vivo model of pathological pain processing.

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The dorsal horn of the spinal cord is a primary pain processing center. In rodent models of neuropathic pain (Hildebrand et al, 2016, Cell Reports) and inflammatory pain (Dedek et al abstract, CAN 2017), we have found that BDNF-mediated loss of synaptic inhibition primes a subsequent potentiation of excitatory NMDAR responses in lamina I neurons of the dorsal horn, resulting in amplified spinal pain signalling. The molecular determinants of lamina I hyperexcitability include downregulation of the KCC2 chloride transporter and STEP61 phosphatase by BDNF, followed by activation of Fyn kinase and potentiation of GluN2B-containing NMDARs. A critical question is whether similar spinal mechanisms of hyperexcitability are conserved during human pathological pain processing. Here, we developed a human ex vivo model of pathological pain using viable human spinal cord tissue that is collected one to four hours post-mortem. We treated lumbar human spinal cord segments with recombinant BDNF or oxygenated saline control and investigated superficial dorsal horn signalling using biochemical and immunohistochemical approaches. Our preliminary western blot data suggests that BDNF treatment results in decreased KCC2 and STEP61 and increased Fyn activation and GluN2B selectively at superficial dorsal horn synapses, similar to that observed in rodent models of neuropathic and inflammatory pain. Thus, we propose that spinal mechanisms of BDNF-mediated hyperexcitability are conserved between rodents and humans and could lead to novel therapeutic approaches for the treatment of pathological pain.

3-B -51 The splicing factor Nova2 regulates action potential threshold in neocortical layer 5 pyramidal neurons

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Nova2, a neuron-specific splicing factor, regulates the expression of neuronal variants of proteins including voltage-gated ion channels. Here we study the role of Nova2 in the intrinsic electrophysiological properties of neocortical layer 5 pyramidal neurons (Ly5PyN) the main cortical output neuron. Recordings in acute brain slices showed significant increase in action potential threshold in Nova2KO Ly5PyN when compared to control mice. Since generation of Ly5PyN action potentials is determined by voltage-gated sodium channels (Nav1.6 and Nav1.2) Nova2 regulation of their expression was assessed. No regulation of Nav1.2 was found. However, two mutually exclusive alternative exons encoding part of segments S3/S4 in the first subunit of Nav1.6 were found to be regulated by Nova2 using high-throughput sequencing of RNA isolated by crosslinking and immunoprecipitation (HITS-CLIP),

exon-junction microarrays and RNA-seq. Exon7 was the primary exon in control cortical transcripts while exon6-containing transcripts were significantly increased in Nova2KOs. Sequence analysis showed high conservation but lack of the negative charge between S3/S4 in the exon6-encoded protein. Total Nav1.6 expression in L5PyN was unchanged, determined by immunohistochemistry. Our results show that Nova2 regulates the action potential threshold of L5PyN through a mechanism that potentially depends on the alternative splicing inclusion of exon7 in the Nav1.6 channel coding sequence. CIHR RNI00109, NIH RO1-NS081706

3-B -52 Modulation of entorhinal cortical input to hippocampal granule cells through activation of local inhibitory network in the dentate gyrus

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Excitatory afferents from the entorhinal cortex (EC) innervate the dentate gyrus and activate simultaneously both glutamatergic and GABAergic cells to trigger a complex interplay between distant excitation and local inhibition. Slow and fast inhibitory signals enable strict spatio-temporal precision that is necessary to achieve high computational power in the dentate gyrus during information processing. In this study, we investigated how recruitment of local inhibitory circuits through perforant path (PP) stimulation could impact EC input integration in granule cells (GC). Slow inhibition is of particular interest as it has the potential to reduce granule cells' excitability and might be involved in shaping their preferential "burst" firing pattern. Our results show that activation of EC inputs can trigger a prolonged inhibitory response that can abolish GC firing for duration of 1-2 seconds. We explored the dynamics of interneuron recruitment by PP inputs and how they shape the long-lasting inhibition observed in granule cells. Balance between direct excitatory signals and the recruitment of disynaptic inhibitory inputs play a critical role in information transfer at the interface of cortical and hippocampal networks.

3-B -53 Neuropeptide signaling affects the glia-neuron interaction during neurodevelopment and is highly associated with neurological disorders

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To maintain the appropriate function of a complex nervous system, the interactions between neurons and glial cells are crucial. Neuropeptides are the major class of neuromodulators only expressed in limited numbers of neurons. We hypothesize that neuropeptides affect the function of glial cells via its receptor. We have shown that inhibition of gene expression in neurons or glial cells using the same RNAi strain results in neurodevelopmental disorders only when Lgr4 is inhibited in glia cells. Lgr4 is classified as a subtype C of the orthologues of the Lgr family and mammalia relaxin receptor RXFP2. Although there is no study of the function of this gene, it is known that the Lgr4 gene is mainly expressed in the CNS and digestive tract in adults and larvae of Drosophila. When Lgr4 was knocked down in neurons at 29 ° C, the animals had no effect on growth, but when Lgr4 was expressed at 29 ° C in glial cells, most Drosophila did not develop into adults. In contrast, the number of the phenotype was reduced to about 50% at 25 ° C. Adult Drosophila grown in the state of Lgr4 knocked down in the glial cell showed low mobility and courtship defect. All these data suggest that Lgr4 expression in glial cells is essential for the early development of Drosophila. The loss of glial cells function is known to be highly related to the onset of neurodegenerative diseases such as epilepsy, Parkinson's disease. Investigating the unknown function of neuropeptide receptors in glial cells is expected to provide a deeper understanding of neurological diseases and neurodevelopment.

3-B -54 Non-ionotropic NMDA receptor activity contributes to the activity-dependent reversal of hyperalgesia and sensitization in pain reconsolidation

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Pathological pain can arise from synaptic plasticity within nociceptive pathways of the spinal cord dorsal horn. We have previously shown that the reactivation of sensitized pain pathways triggers a process that parallels memory reconsolidation, in which potentiated synapses undergo a simultaneous process of potentiation and depotentiation prior to restabilization. Isolating the depotentiation process can reverse synaptic potentiation and erase hyperalgesia. Reconsolidation is crucially dependent on NMDA receptor activity. NMDA receptors have both ionotropic and non-ionotropic effects that are associated with synaptic potentiation and depotentiation, respectively. We hypothesize that non-ionotropic NMDA activity (NI-NMDA) mediates depotentiation in pain reconsolidation. Whole-cell patch clamp in spinal cord slices and explants were used to study long-term potentiation (LTP) in the dorsal horn. Mechanical sensitization was induced in behavioural studies by injection of capsaicin in the hind paw. The combination of neuronal activity and pharmacological isolation of NI-NMDA via 7-chlorokynurenate (7-CK) caused the reversal of dorsal horn LTP but did not reverse LTP alone. Behaviourally, intrathecal administration of 7-CK in combination with plantar capsaicin reversed mechanical hyperalgesia, while nonspecific blockade of NMDA activity did not. These data indicate a key role for NI-NMDA in pain reconsolidation and identify this signaling pathway as a potential novel target for lasting relief.

3-B -55 Connectivity and network state-dependent recruitment of long-range VIP-GABAergic neurons in the mouse hippocampus

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GABAergic cells with long-range axonal projections (LRP) to distant areas are involved in coordination of functionally related brain regions. However, the connectivity pattern and recruitment of these cells in vivo in awake animals remain largely unknown. Here, we examined connectivity and the network state-dependent recruitment of the vasoactive intestinal peptide (VIP)-expressing neurons whose axon innervates CA1 and projects to the subiculum (VIP-LRPs). Using the channelrhodopsin2-based antidromic activation of VIP-LRPs cells in slices obtained from VIP-Cre-Ai32 mice, we examined the VIP-LRP targets in the hippocampal CA1 area. Our data showed that VIP-LRP cells preferred to target GABAergic interneurons, contacting the oriens-lacunosum moleculare and bistratified cells in the CA1 oriens/alveus, and the Schaffer collateral-associated and basket cells in the stratum radiatum. Using two-photon calcium imaging in awake head-fixed VIP-Cre mice in combination with local field potential recordings and post-hoc neurochemical identification, we examined the activity of VIP-LRP cells during different brain states. The data showed that these cells were mostly recruited during quiet wakefulness; however they were not coupled to sharp-wave ripples. Taken together, these data indicate that VIP-LRP neurons prefer to contact different types of inhibitory interneurons in the hippocampal CA1 area and may coordinate the hippocampo-subicular information flow during animal quiet states.

3-B -56 Characterizing dendritic chloride distribution and entry using fluorescence lifetime imaging microscopy

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Chloride (Cl-) homeostasis is crucial for neuronal signaling - it regulates intrinsic excitability by tuning the magnitude of γ-aminobutyric acid type A (GABAA) receptor currents, and controls cell volume as a key contributor to cytosolic tonicity. As such, Cl- gradients across the plasma membrane are tightly constrained by a host of membrane transporters. Studying the impact of Cl- flux on physiological processes is challenging due to the technical limitations of clamping intracellular Cl- with whole-cell patch clamp and the lack of robust fluorescent imaging tools. To the latter, the best available Cl-sensitive fluorophore is the quinoline-based dye N-(Ethoxycarbonylmethyl)-6-Methoxyquinolinium Bromide (MQAE), which decreases its fluorescence emission with increasing Cl- and is susceptible to photobleaching. MQAE is, however, suitable for quantification of intracellular [Cl-] using fluorescence lifetime imaging microscopy (FLIM). Here we sought to determine whether subcellular Cl- entry in dendrites could be quantitatively measured in response to excitatory activity, as it would glean insights into Cl- driven cellular swelling (edema). We patch-filled cortical pyramidal neurons (layer 4) with MQAE to pair whole-cell electrophysiology with FLIM, enabling us to map dynamic shifts in dendritic [Cl-]i and commensurate changes in volume at single-spine resolution. We show that membrane depolarization increases [Cl-]i by MQAE lifetime measurement, with dramatic [Cl-]i dysregulation and localized dendritic beading when combined with 10µM N-methyl-D-aspartate (NMDA) stimulation.

3-B -57 Optogenetic kindling of neocortex elicits seizures

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We developed a novel optogenetic kindling model of epilepsy to investigate how cortical circuits are affected by seizures. After expressing Channelrhodopsin-2 bi-hemispherically in pyramidal cells (PCs) of primary motor cortex, we stimulated awake, freely behaving mice every 48 hours with fiber-coupled 445-nm lasers while recording video and EEG. To look for changes in layer-2/3 (L2/3) PC properties, we carried out whole-cell recordings in acute slices from stimulated and control animals. Seizures were elicited after ~13 sessions in 6 out 6 animals. We found that seizure duration and severity, as well as number of seizures increased over sessions, while seizure threshold decreased. Additionally, seizure susceptibility was retained when stimulation was paused for 36 days. After this pause, seizures re-emerged more rapidly and with greater intensity. L2/3 PC recordings revealed an increase in spike after-hyperpolarization, half-width, and height relative to controls. By immunostaining for GFAP and NeuN, we did not find gross neuronal damage nor significant glial activation in stimulated versus control animals but we did observe an increase in glial activation in injected versus control cortex across all animals. Our results show that repeated optogenetic stimulation of otherwise healthy brains can lead to seizures and that animals show elevated seizure susceptibility for weeks. Changes in seizure dynamics may be partially explained by changes in intrinsic properties, as we didn't find any injuries or gross brain damage in stimulated animals.

3-B -58 Functional behaviour of brain-specific Nav1.5 voltage-gated sodium channels

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The voltage-gated sodium channel Nav1.5 contributes to cell excitability in both the heart and brain. Nav1.5 is subject to alternative splicing at exon 6, such that Nav1.5 retains exon 6b while the splice-form Nav1.5e acquires exon 6a instead. Whereas in the heart Nav1.5e expression peaks in neonates and is absent postnatally, in the brain we find that expression persists into adulthood. This alternative splicing may have repercussions on neuronal firing, given that the main difference is a 10 mV depolarizing shift

in the activation profile of Nav1.5e relative to Nav1.5. The two splice-variants differ at 7 amino acid residues, all of which are located in the voltage sensor of domain I. Even though these residue exchanges occur in a part of the channel which is critical for pore opening, their specific structure-function relationships are not fully explored. We engineered single point mutations, introducing key amino acids from Nav1.5e into Nav1.5, and identified three residues contributing to the altered activation profile. Moreover, we identified one residue which increases the propensity for inactivation, despite the fact that inactivation is thought to be mediated by domain IV. This study illustrates the mechanism by which alternative splicing in domain I modulates the functional properties of Nav1.5, which may contribute to the fine-tuning of cell excitability.

3-B -59 Spreading Depolarization Evoked by Ischemia in Cortical Slices of the Frog

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Anoxia in mammals and insects an abrupt shutdown of higher CNS gray matter as a result of spreading depolarization (SD) but it is unclear if SD is generated in the cerebral cortex (CC) of lower vertebrates. In this study, the effects of oxygen glucose deprivation (OGD) on live coronal brain slices from frogs was compared to rats to better understand the evolution of SD and susceptibility of a cold-blooded species to SD. We examined whether frog CC can generate SD and if so, its propensity to initiate compared to rat. Light transmittance (LT) imaging was used to determine SD onset time and neuronal damage in response to OGD, ouabain (100 uM) or elevated [K+]o, at several temperatures. Frog CC underwent OGD-SD after a mean of 11 min (6 slices) at 35oC but with high variability (sd = ±9 min). This onset was delayed and was more variable compared to rat slices where onset time was ~3 min (16 slices) at 35oC. Frog CC underwent ouabain-SD after a mean of 5.6 min (sd = ±1.06 min, 12 slices) at 35oC compared to 4.8 min on average (120 slices) in rat CC as shown previously in our lab. Unlike in rat, SD was not evoked in frog CC by elevating [K+]o to 26mM at 26oC (8 slices), 32oC (6 slices) or 35oC (8 slices). Our findings show that the capacity to generate SD in the cerebral cortex evolved early in vertebrate evolution, but that the propensity to initiate SD appears greater in rat versus frog at 35oC.

3-B -60 Regulation of transmitter release through the CaV2 alpha 1 C-terminal EF-hand F-helix tyrosine

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The CaV2 calcium current is the target of both excitatory and inhibitory regulation of transmitter release at Aplysia synapses with GPCR activation. To examine the mechanisms underlying this regulation, we cloned the Aplysia CaV2 calcium channel subunits. While a variety of splice variants exist in the whole animal nervous system, the mechanosensory neurons preferentially express a distinct CaV2a1 subunit. Generating RFP-tagged recombinant CaV2a1 subunits, we confirm expression and replacement of the endogenous CaV2a1 subunit in sensory neurons. We examined the tyrosine kinase inhibition of the CaV2 current with a CaV2a1 C-terminal EF-hand F-helix tyrosine to phenylalanine point mutant, demonstrating that phosphoregulation of this site is highly conserved. Since the CaV2 current is solely responsible for triggering action-potential evoked transmitter release at these synapses, we further examined the impact of the CaV2a1 Y/F point mutant on dopaminergic and 5HT1A-mediated inhibition.

3-B -62 Elfn1 interactions with mGlu7 and GluK2 determine layer-specific synaptic properties onto cortical interneurons

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Excitatory synapses onto somatostatin (SOM) interneurons show dramatic short-term facilitation. Previous work has shown that Elfn1 (extracellular leucine-rich repeat fibronectin containing 1) is necessary to generate facilitating synapses onto SOM neurons. Using Elfn1 knockout mice, we show that generation of the striking facilitation seen in CA1 hippocampal and cortical layer 2/3 (L2/3) SOM neurons can be attributed to Elfn1 recruitment of two separate presynaptic components: metabotropic glutamate receptor 7 (mGluR7), and glutamate receptor, kainate subunit 2 containing kainate receptors (GluK2-KARs). First, mGluR7 transynaptically interacts with Elfn1, constitutively activating mGluR7 and reducing initial release probability. In contrast, the strong facilitation that then emerges late in a spike train is mediated by GluK2-KARs. Notably, synapses onto layer 5 (L5) cortical SOM interneurons facilitate less than in L2/3, are less affected in Elfn1 knockout, and are insensitive to the GluK2-KAR antagonist NS-102. Thus layer specific synaptic properties onto SOM interneurons are mediated by differential recruitment of mGluR7 and GluK2-KARs, and reveal a mechanism that generates a diversity of physiological responses in interneurons.

3-B -63 Homeostatic-like Potentiation of the Aversive Habenulo-Raphe Pathway in an Animal Model of Post-Stroke Depression

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Stroke is the third leading cause of death and the primary cause of adult long-term disability in Canada. Despite advances in rehabilitation research, stroke survivors experience an unusually high incidence of depressive symptoms which, beyond the emotional suffering, also undermine recovery outcomes by reducing patient motivation levels. Human and animal studies have linked the incidence of post-stroke depression to the extent of prefrontal cortex (PFC) damage. We hypothesized that PFC stroke promotes the development of depressive phenotypes by triggering maladaptive reorganization in mood-related networks. The PFC and the lateral habenula (LHb) are limbic structures that both control the serotonergic dorsal raphe nucleus (DRN), a key neuronal hub for mood regulation. We used viral, optogenetic and electrophysiological strategies to outline the functional architecture of the PFC and LHb projections to DRN. We found that a PFC stroke triggers a time-dependent remodeling of key functional features of the glutamatergic input from the LHb to DRN 5-HT neurons. Because the LHb-DRN pathway is believed to encode emotional features such aversion and anticipation of threat, a maladaptive, homeostatic-like, upregulation of this pathway may contribute to the depressive symptomology following a stroke.

3-B -64 Optogenetic approach for the study of chloride homeostasis

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Chloride homeostasis is central to maintaining proper GABAA-mediated inhibition. In the adult CNS, the K+-Cl- cotransporter KCC2 is the main Cl- extruding to maintain low intracellular [Cl-] in neurons. Accumulating evidences confirm that several pathologies and debilitating conditions result from loss of KCC2 function leading to impaired Cl- homeostasis and ensuing abnormal inhibition. Thus, methods to accelerate and facilitate the study of Cl- homeostasis are crucial for the development of new therapeutics. Single cell patch-clamp measurements of GABAA reversal potential remain the gold standard to study Cl- homeostasis. Yet the approach still has limitations. Among those it is still not possible to modulate "at will" the intracellular Cl- concentration to test the extrusion capacity of KCC2

under normal or challenging conditions like those observed in pathological state. One of the leading strategies is the imposition of a Cl- load through a patch clamp recording pipette, which results in continuous KCC2 activation, introducing potential confounding factors. To circumvent this, we developed a protocol using the light-gated Cl- pump Halorhodopsin (NpHR) to induce a transient Cl- load. Using this approach, we have been able to measure the rate of recovery of evoked Cl- currents following the end of the light-activated Cl- load. This yields an effective measure of the Cl- extrusion capacity of the cells under functional conditions. The approach was tested in vivo using a micro-optrode we previously designed as well as in vitro in primary neuronal cultures and slices.

3-B -65 Caught in the act: In vivo 2-photon imaging evidence of phagocytosis of synapses in the Xenopus laevis retinotectal circuit

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There is accumulating evidence suggesting that microglia play an active role in synaptic pruning. However, while microglia are known to survey and contact synapses, real time evidence of microglia removing material from synapses has yet to be observed. Indeed, microglia may be arriving to clean up material from dead cells. Alternatively, pruned synapses may be ejected and microglia are simply passing by after the event has occurred to collect synaptic debris. The Xenopus laevis retinotectal circuit was used. Microglia were labelled by intraventricular injection with Alexa 594 conjugated to IB4-isolectin. To label RGC axons, RGCs were electroporated with eGFP plasmids, a mixture of 5% Alexa 488 dextran and 0.5% pHrodo green dextran, or plasmids expressing a pH-stable GFP. In long-term imaging studies, all analysis excluded any animals where axonal loss was detected. Morphologically, microglia in Xenopus larvae resemble the amoeboid microglia which have been described in neonatal rodents. Time lapse imaging demonstrated that microglia move at speeds between 1 to 10 µm/min. Contact between microglia and axons was observed. When axons were labelled with dextrans or with pH-stable GFP, microglia could be observed becoming more fluorescent after contact with labeled axons in real time. Long-term imaging studies over several days using pH-stable GFP also demonstrated a significant accumulation of green fluorescent material in microglia. This study provides evidence to support the hypothesis that microglia play active roles in synaptic pruning.

C – Disorders of the Nervous System

3-C -66 Disruption of autophagic signaling in murine forebrain affects excitatory-inhibitory balance via mistrafficking of GABAA receptors leading to ASD-like behaviours

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Many monogenic forms of autism spectrum disorder (ASD) are known to affect the mTOR pathway. While recent work has focused on the dysregulation of protein translation, few studies have examined how disruption of autophagy, another major downstream branch of mTOR signaling, contributes to neuronal dysfunction and ASD pathogenesis. As ASD is believed to be caused by an imbalance between excitatory and inhibitory signals in the brain, we have developed mutant mice with autophagy deficiency in either forebrain excitatory or GABAergic inhibitory neurons using CaMKII-cre and Dlx5-cre for Atg7 deletion. A time-dependent formation of p62+ aggregates was observed in affected neurons in the cerebral cortex, hippocampus, and striatum of these mice. Interestingly, both CaMKII-cre and Dlx5-cre

Atg7 cKO mice exhibit a similar set of ASD-like behavioural abnormalities. Furthermore, we have detected a disruption in the excitatory-inhibitory balance of both knockout mice. Consistently, a reduction in the surface expression of GABAA receptors was observed in primary neurons with Atg7 deletion. Immunofluorescence examination of GABA receptor-associated protein-like 2 (GABARAPL2) and its related family members shows that they are mislocalized to p62+ aggregates in affected neurons in both Atg7 cKO mice. Knockdown of GABARAPL2 in primary neurons similarly showed reduced surface expression of GABAA receptors, thus suggesting that the loss of functional GABARAPL2 in Atg7 cKO neurons may be the causal link to the disruption of E-I balance and abnormal ASD-like behaviours observed in Atg7 cKO mice.

3-C -67 Toll-like receptors 4 and 9 expression change in rodent model of epilepsy

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Rationale: Toll-like receptors (TLR) are innate immune receptors that are important in early host defense against pathogens. TLRs recognize pathogen- or damage-associated molecular patterns (PAMPs/DAMPs). TLR4 is expressed on the cell surface and is most well known for recognizing lipopolysaccharide (LPS), a marker of bacteria. TLR9 is expressed intracellularly and recognizes unmethylated CpG DNA motifs, characteristic of DNA viruses, and prokaryotic genomes. TLR4 has been implicated in both experimental and human epilepsy; TLR9 has yet to be studied. Here we investigated the gene expression changes of TLR 4 and 9 during epileptogenesis and chronic epilepsy rodent models. Methods: Freely moving male Sprague-Dawley rats (n=4 per group) received systemic administration of kainate and lorazepam (KaL). Rats were sacrificed after 4 days, 14 days, or 20 weeks, and whole hippocampi were removed. qPCR was performed for TLRs 4, and 9 on an ABI StepOnePlus instrument with custom-designed primers. Cq values (technical replicates) were averaged and geometric means were calculated. Relative gene expression changes of (TLRs) 4 and 9 were calculated using REST software (Pfaffl method). Results: The 4 d KaL group showed increased expression of both TLRs, which was further enhanced at 14 d. TLRs in the chronic KaL group (20 weeks) was up-regulated, but slightly less than the epileptogenesis group. Conclusion: TLR 4 and 9 expressions is enhanced and prolonged during epileptogenesis. These data warrant the further investigation on the role of these TLRs in epilepto- and ictogenesis.

3-C -68 THE EFFECTS OF OF RELAXIN-3 AND A SPECIFIC RXFP3 AGONIST ON FOOD INTAKE AND CIRCULATING HORMONES IN RATS

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Relaxin-3 is a neuropeptide produced by GABA neurons in specific brain areas, including nucleus incertus, and is implicated in motivated behaviours and stress responses. Relaxin-3 preferentially activates the Gi/o-protein-coupled receptor, RXFP3, but can activate RXFP1, the cognate Gs-protein-coupled receptor for relaxin. Conversely, the truncated peptide, RXFP3-A2 (A2), is a highly-selective RXFP3 agonist. In this study we assessed the responses to central administration of relaxin-3 and A2 on feeding and circulating hormone levels in male rats. Acute intracerebroventricular injection of relaxin-3 and A2 (1.1 nmol) increased food intake, with a more rapid response to A2 (relaxin-3, $p \leq 0.0054$ vs A2, $p \leq 0.0001$ after 30 min). Relaxin-3, but not A2 increased water intake, and increased plasma testosterone and corticosterone ($p \leq 0.0001$, 60 min post-injection) suggesting a role for RXFP1, but not RXFP3. In addition, in situ hybridization studies revealed different patterns of c-fos mRNA expression in the

paraventricular hypothalamic nucleus, supraoptic nucleus and medial preoptic area of relaxin-3 vs A2-treated and vehicle-treated rats. In contrast, both icv relaxin-3 and A2 increased c-fos mRNA levels in the lateral hypothalamic area. These results further illustrate the differential pharmacological effects of RXFP1 and RXFP3 activation on key hypothalamic networks regulating feeding and the hypothalamic-pituitary-gonadal axis. Ongoing studies aim to determine which of these effects represent physiological actions of relaxin-3 signalling at RXFP1 and/or RXFP3.

3-C -69 Treatment with an interleukin-1 receptor antagonist improves neurological outcomes in an experimental model of polytrauma

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Objective: Traumatic brain injury (TBI) and bone fracture are common components of polytrauma. This injury combination in mice results in elevated levels of the pro-inflammatory cytokine interleukin-1β (IL-1β) and exacerbated neuropathology when compared to isolated-TBI. Here we examined the effect of treatment with the IL-1 receptor antagonist (IL-1ra), Anakinra, in mice given a TBI and tibial fracture. Methods: C57BL/6 mice were given either sham injuries or polytrauma (i.e., closed head TBI and tibial fracture) and then treated with either saline-vehicle or IL-1ra (100 mg/kg). Treatments were subcutaneously injected at 1, 6, and 24 hours, and then daily for one week post-injury. 7-8 mice/group were euthanized at 48 hours post-injury. To assess long-term recovery, 12-16 mice/group underwent behavioral testing at 12 weeks post-injury and in vivo MRI at 14 weeks post-injury before being euthanized at 16 weeks post-injury. Post-mortem analyses assessed neuroinflammation and cerebral edema. Results: Activated microglia and astrocytes, as well as edema, were decreased in polytrauma mice treated with IL1-ra compared to polytrauma mice treated with vehicle. MRI indicated that IL-1ra treatment mitigated volumetric loss in the injured cortex as well as track-weighted MRI markers for axonal injury. Interpretation: Treatment with the IL-1ra, Anakinra, reduced neuroinflammation, edema, and brain damage in mice given TBI and tibial fracture. Anakinra is approved for human use and may represent a promising treatment in polytrauma cases that involve TBI and fracture.

3-C -70 Electron microscopic evidence of markers of premature aging in the PS-1(M146V) mouse model of Alzheimer pathology

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Alzheimer's Disease (AD) is characterized by the accumulation of β-amyloid (Aβ) peptide, which can deposit as "plaques" in the brain. Yet, the role of Aβ, although it is neurotoxic, remains ambiguous. Pre-symptomatic stages of AD are associated with neuropathic changes that precede the more easily identified amyloid plaques. Our ongoing research aims to identify when, and where such early changes occur in the brain. To characterize the early pathological changes that are independent of Aβ or plaque formation, we used a mouse model of AD that harbours a familial AD-linked mutation in presinillin-1: PS-1(M146V). Previous work of ours based on transmission electron microscopy (TEM) concluded that neuronal pathologies were seen at 6 months (6 mo), but not at 3 months (3 mo), while vascular pathology was observed at 3 mo. We hypothesized that in regions with observed volume reductions - the entorhinal cortex, but not the hippocampus - in 3 mo-old PS-1(M146V) mice, there would be Aβ-independent acceleration of age-related vessel changes that would not normally be observed until later. Using TEM we found a lack of significance in astrocyte coverage in the 6 mo homozygote (HO) mice

suggesting there is abnormal astrocyte coverage in the entorhinal cortex at 6 mo, but not at 3 mo. There is no significant difference in basement membrane thickness (BMT) in the entorhinal cortex between wild type (WT) or HO, or 6 mo and 3 mo. We concluded the pathology that appears first when comparing BMT and astrocyte coverage in PS-1(M146V) mice is abnormal astrocyte coverage.

3-C -71 IL-17A in the peripheral blood and hippocampi of rats chronically exposed to low doses of ozone

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Exposure to low doses of O3 leads to a state of oxidative stress. Some studies show that oxidative stress state can modulate both CNS and systemic inflammation, which are important for the development of Alzheimer Disease (AD). The aim of this study was to evaluate changes in the frequency of Th17-like cells (CD3+CD4+IL-17A+), the concentration of IL-17A in the peripheral blood, and hippocampus immunoreactivity to IL-17A of rats exposed to low doses of O3. One hundred and eight male Wistar rats were randomly divided into 6 groups (n=18) with the following treatments: control (O3 free), and O3 exposure groups (0.25 ppm, daily 4h) for 7, 15, 30, 60, 90 days. From each group 12 of the animals were decapitated and a peripheral blood sample was taken for isolation of plasma and mononuclear cells. Plasmatic IL-17A was quantified by LUMINEX, while the frequency of Th17-like cells was evaluated by flow cytometry. The resting 6 rats were deeply anesthetized, and transcardially perfused for the immunofluorescence technique in the hippocampus. Our results show that 7-day exposure to O3 produces a significant increase in the frequency of Th17-like cells and levels of IL-17A in peripheral blood. However, a decrease of Th17/IL-17A is observed from 15 days of exposure. We also found an increase of IL-17A in the hippocampus after a 60- and 90-day exposure. These results indicate a short-term Th17-like/IL-17A systemic effect induced by O3, and an increase of IL-17A in the hippocampus tissue during the chronic neurodegenerative process. This work was supported by CONACyT-219703 to SR-A.

3-C -72 Excessive Temporomandibular Joint Overloading Leads to Neuropathic Orofacial Pain in Mice

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Temporomandibular joint disorder (TMD) is a set of degenerative musculoskeletal conditions characterized by pain in temporomandibular joints (TMJ) and/or masticatory muscles. It is one of the most common causes of chronic orofacial pain, affecting up to 25% of the population. However, the underlying mechanism is unknown. Here, we reported a novel mouse model of TMD. With excessive TMJ overloading, mice developed acute and chronic orofacial mechanical hypersensitivity and TMJ dysfunction. Mice also exhibited masseter muscle dystrophy with local inflammation, neuronal damage in trigeminal afferent, and increased macrophages and microglia activation in trigeminal ganglia and trigeminal nucleus caudalis respectively. Treatment with CSF-1 receptor inhibitor PLX5622 attenuated macrophages and microglia activation and inhibited orofacial mechanical hypersensitivity. These results shed light on the potential relationship between neuroinflammation and TMD.

3-C -73 CHARACTERISTICS OF MONOCYTES AND MACROPHAGES IN B7.2 TRANSGENIC MICE DEVELOPING SPONTANEOUS AUTOIMMUNE PERIPHERAL NEUROPATHY

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Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are prototypical autoimmune peripheral neuropathy (APN) which affects millions of people worldwide. Although disease underlying mechanisms remain elusive, T lymphocytes and macrophages are recognized as major players in mediating autoimmune response leading to destruction of peripheral nervous system. We recently established a novel and clinically relevant animal model of APN. B7.2 transgenic L31 mice spontaneously develop neurological symptoms. Massive infiltration of CD8 T cells and macrophages is found in diseased nerves. In this study, we aim to characterize monocytes/macrophages in L31 mice to better understand the critical roles of macrophages in disease pathogenesis. We found that 1) in the blood of L31 mice, even before disease onset, the frequency of CD115+ monocytes is significantly higher than in control littermates. The majority are CCR2+ pro-inflammatory monocytes; 2) in peripheral nerves of both pre-symptomatic and symptomatic L31 mice; macrophage frequency is higher than in control mice with an increased CX3CR1 expression. CX3CR1+ macrophages are responsible for enhanced phagocytic activity; 3) increased B7.2 expression was found mainly on CX3CR1+ macrophages. These data suggest that L31 mice have a predisposed inflammatory environment. Macrophages in peripheral nerves are activated. They promote disease with enhanced B7.2 expression and increased phagocytic capability. Further functional analysis will be performed in L31 mice deficient in either CCR2 or CX3CR1.

3-C -74 Dynamic nature of olfactory bulb atrophy and early caspase activation in the BACHD rat models

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Olfactory dysfunction is observed in several neurological disorders, including Huntington disease (HD), and correlates with global cognitive performance, depression and degeneration of olfactory brain regions. Despite clear evidence demonstrating olfactory dysfunction in HD patients, only limited details are available in murine models and the underlying mechanisms are unknown. In order to determine if alterations in the olfactory bulb (OB) are observed in HD we assessed OB weight from 3 to 12 months of age in the BACHD rat models (TG5 and TG9). A decrease in OB weight was observed at 6 and 12 months of age compared to WT (ANOVA $p=0.02$). Despite no differences in OB huntingtin mRNA levels between the BACHD lines, we observed an increase in OB mutant htt protein expression in line TG5 vs. TG9 ($p<0.01$), and a decrease in htt levels in TG9 vs. WT ($p<0.05$). We then characterized caspase (casp) expression levels at 3, 6 and 12 months. We observed a significant increase in casp3, 6 and 8 mRNA levels early in line TG9 ($p<0.05$). In contrast, casp9 mRNA levels were decreased in TG9 ($p<0.05$) at 3 months and TG5 by 6 months ($p<0.05$). The p20p10 form of casp6 was decreased in both TG5 and TG9 OBs early (suggesting activation of casp6, ANOVA $p=0.003$), and an increase in active casp8 fragments detected in both lines (ANOVA $p=0.003$). A decrease in the proform of casp9 was observed in 12 months TG9 OB vs. WT (ANOVA $p=0.003$). Identification of early markers for HD will help inform therapeutic approaches and will clarify the utility of olfactory function testing in at risk HD individuals.

3-C -75 Assessment of astrocyte-oligodendrocyte coupling integrity in the brain of depressed suicides

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Imaging studies have shown widespread changes in white matter integrity and brain connectivity in patients with major depressive disorder, in agreement with reports of altered oligodendrocyte (OL) densities in human postmortem studies and impaired myelin ultrastructure in animal models of depression. Myelination of axons by OLs is tightly regulated, notably by astrocytes (AS), which establish

gap junctions with OLs through heterotypic coupling of AS-specific (Cx30 and Cx43) and OL-specific (Cx32 and Cx47) connexins, allowing metabolic support to OLs. This study aims to investigate if changes in myelin integrity associated with depression can be linked to abnormal astrocyte-oligodendrocyte coupling. Using postmortem samples from depressed suicides and matched controls, we screened the expression of the 4 major connexins involved in the formation of both cell-specific and AS-OL gap junctions in brain areas previously associated with changes in OL function. Of note, we only found a robust decrease in the expression of the AS-specific Cx30, observed specifically in the dorsolateral prefrontal cortex. Changes in homotypic and heterotypic connexin coupling are being quantified by co-immunoprecipitation. Finally, immunofluorescence and confocal microscopy is being used to anatomically characterize AS-specific connexin pairing with myelinated axons. Given that glial pathology is a major hallmark of depression, understanding how glia-glia interactions shape oligodendrocyte function in health and disease may prove useful in understanding the neurobiological basis of mood disorders.

3-C -76 Chronic metformin treatment downregulates hyperactivated ERK signaling in the forebrain, but not in hindbrain and peripheral tissues in the Fragile X Syndrome (FXS) mouse model

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Fragile X Syndrome is the most common form of hereditary intellectual disability and a leading single gene cause of autism. Impaired translational mechanisms represent one of the features of FXS. We studied total and phosphorylated ERK by Western blot in the prefrontal cortex (pfc), hippocampus (hipp), striatum (str), cerebellum, gonads and liver of adult male wild-type (WT) and fmr1 KO mice treated with metformin for 10 days (200 mg/kg, i.p.). We also examined upstream MEK, b-Raf and c-Raf proteins in hipp. To study metformin actions, we examined activation of AMPK and its substrates ACC1, Raptor and TSC-2. In addition, we injected a single dose of metformin (200 mg/kg) and assessed AMPK activation in hipp 0, 0.5, 1, 2 and 4 h after the treatment. Metformin concentrations in the brain and plasma were determined by LC-MS/MS. We determined ERK hyperactivation in fmr1 KO compared to WT mice in all examined tissues except gonads. Chronic metformin treatment downregulated p-ERK in pfc, hipp and str, and downregulated p-MEK, b-Raf and c-Raf in hipp. We did not observe activation of AMPK and its substrates after chronic treatment in hipp. However, a single metformin injection activated AMPK 2 h after administration. Metformin concentrations in the plasma and brain were highest 0.5 h after the injection and slowly declined afterwards. The results from this study provide knowledge in the signaling mechanisms that contribute to impaired translational control in FXS and might introduce new pharmaco-therapeutical directions for the prevention of developmental impairments in FXS.

3-C -77 Auditory oddball training improves prepulse inhibition in a mouse model of schizophrenia

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The use of computer-based cognitive training for patients in order to ameliorate cognitive deficits in schizophrenia has increased in recent years. However, as this has been a highly heterogeneous approach, the results have been mixed, and the neurological underpinnings of these trainings remain largely unknown. To study the effect of an auditory oddball training in an animal model of schizophrenia, we used serine racemase (SR) -/- mice, which lack the conversion of L-serine to D-serine.

These mice are known to have prepulse inhibition (PPI) deficits, a measure of a pre-attentive filtering mechanism that is also deficient in schizophrenia and may potentially contribute to cognitive deficits. Our goal was to test whether training SR -/- mice in an adaptive oddball task could restore PPI deficits. First, we replicated the finding that SR -/- mice have lower PPI (main effect genotype $p < 0.05$). Mice were then divided in training and sham groups. We observed that SR -/- performed worse in the oddball task, reaching lower levels throughout training (main effect $p < 0.01$). Interestingly, training didn't change PPI in SRR +/+ mice (t test $p > 0.05$) but improved PPI in SR -/- (t test $p < 0.05$). D-serine (i.p.) added to training increased the performance of SR -/- mice in the oddball task (main effect $p <0.01$). Our results show for the first time that a cognitive training strategy can improve PPI in an animal model of schizophrenia. We will now determine whether cognitive training can also improve PPI in patients with schizophrenia and whether this correlates with cognitive gains.

3-C -78 Mitochondrial-derived vesicles in neurons: implications for mitochondrial quality control and Parkinson's disease

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Mitochondrial quality control (QC) mechanisms have evolved to ensure the maintenance of a healthy mitochondrial population, which is essential for normal neuronal function. PINK1 and Parkin, which are mutated in autosomal recessive forms of Parkinson's disease (PD), mediate the removal of damaged mitochondria by autophagy (mitophagy). Our lab recently demonstrated that PINK1 and Parkin regulate a distinct mitochondrial QC pathway, the generation of a subtype of mitochondrial derived vesicles (MDVs) in response to oxidative stress. PINK1/Parkin-dependent MDVs shuttle damaged mitochondrial cargo to the lysosome for degradation. We hypothesise that MDVs are crucial for neuronal health and are the first line of mitochondrial QC, eliminating damaged mitochondrial components before sufficient damage accrues to induce mitophagy. Whole-scale removal of mitochondria, as occurs during mitophagy, may be detrimental to neurons given their high energy demand. However, MDVs have not yet been studied in neurons. Utilizing human induced pluripotent stem cells (iPSCs) to differentiate neurons, we undertook to study MDVs for the first time in a neuronal system. Preliminary data indicate that MDVs are formed basally in cultures of different neuronal types (dopaminergic, cortical and motor neuronal cultures). Future investigations will focus on dissecting the MDV pathway in neurons and using iPSCs derived from patients with PD to study whether the pathway is abrogated in diseased neurons. This work will provide new insights into the role of MDVs in mitochondrial QC in neurons and in PD.

3-C -79 Neuroprotective and immunomodulatory effects of two 5alpha-reductase inhibitors in the myenteric plexus of a mouse model of Parkinson's disease

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Motor symptoms in Parkinson s disease (PD) are often preceded by gastrointestinal disorders associated with the alteration of dopaminergic (DA) neurons in the myenteric plexus (MP). Studies in our laboratory have demonstrated the immunomodulatory effect of female hormones to treat enteric neurodegeneration in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD. The aim of this project was to evaluate the neuroprotective and anti-inflammatory role in the MP of two 5α-reductase inhibitors, Finasteride (FIN) and Dutasteride (DUT), for which a mitochondrial effect has also been reported. Adult male C57BL/6 mice received 1 daily injection of FIN or DUT (5 or 12.5 mg/kg). On day five, 4 injections of MPTP (6.5 mg/kg) were administered. On day ten, mice were killed, the ileum was fixed and microdissected to isolate the MP. Cuprolinic blue staining and

immunohistochemistry with tyrosine hydroxylase (TH) and ionized calcium-binding adapter molecule 1 (Iba1) antibodies were performed for stereological counting of total neurons, DA neurons (TH+) and macrophages (Iba1+). In vitro, free radicals, nitric oxide and pro-inflammatory cytokines production, mitochondrial fragmentation and nuclear factor-kappa B (NF-κ?B) response, following 1-methyl-4-phenylpyridinium (MPP+) treatment, were also measured for each condition. Overall, our results suggest that DUT may help prevent the loss of DA neurons, the infiltration of macrophages and pro-inflammatory responses.

3-C -80 Using zebrafish to throw light into the role of DEPDC5 in epilepsy

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Mutations in the DEP-domain containing 5 (DEPDC5) protein, which forms a part of the mTOR inhibiting GATOR1 complex and is highly conserved in vertebrates, were recently found to be a cause of familial focal epilepsy. However, the role of DEPDC5 in neuronal processes and hence its relevance to epilepsy remains unclear. Zebrafish, owing to the ease of manipulation at early stages of development, along with the transparency of the embryos and the advent of powerful genetic tools, has emerged as a popular model to study development and disease. We have disrupted the highly conserved Domain of Unknown Function DUF3608 of zebrafish depdc5 gene using CRISPR genome editing and confirmed the knockout at genomic, RNA and proteins levels. Knocking out DEPDC5 is lethal, as homozygotes do not survive beyond two weeks post-fertilization. While the depdc5-/- embryos do not show obvious epileptic behavior upon continued monitoring in light-dark cycles, they do show hypoactivity during the light cycles specifically. RNA deep sequencing analysis and studies using in vivo calcium reporters are underway to further pinpoint subtle epileptic foci and ultimately to understand the role of DEPDC5 in focal epilepsy. This model would also be useful in testing new drugs against refractory epilepsy, since patients carrying DEPDC5 mutations have been observed to be non-responsive to conventional anti-epileptic drugs.

3-C -81 Dopaminergic neurodegeneration in a rat model of chronic hyperglycaemia

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Hyperglycaemia is known to cause oxidative stress, which can in turn damage the nervous system. Accumulating epidemiological data show a correlation between diabetes and neurodegenerative disorders, including Alzheimer?s disease and Parkinson?s disease. We recently demonstrated that physiologically elevated levels of glucose lead to the death of dopaminergic neurons in culture through oxidative and apoptotic mechanisms. In this respect, the goal of this study was to characterize dopaminergic neurodegeneration in a rat model of chronic hyperglycaemia. In addition, we investigated the presence of neuroinflammation around brain regions densely populated with dopaminergic neurons. Rats were injected with streptozotocin, a toxin that destroys insulin-producing pancreatic beta cells. The presence of abnormal plasma insulin levels, glycated haemoglobin, glucose tolerance, polyuria, polydipsia, and polyphagia confirmed the hyperglycaemic status of the rats. Three or six months after the induction of hyperglycaemia, rats were sacrificed and brain tissues were harvested to perform immunoblotting and immunohistochemistry. Our data demonstrate the presence of dopaminergic neurodegeneration and neuroinflammation six months after streptozotocin injections. In particular, levels of tyrosine hydroxylase, a key enzyme in dopamine synthesis, were reduced in the midbrains of hyperglycaemic rats. These results suggest a relation between hyperglycaemia and dopaminergic

neurodegeneration, providing new insight on the higher occurrence of Parkinson?s disease in diabetic patients.

3-C -82 The Metabotropic Glutamate 2 Receptor Positive Allosteric Modulator LY-487,379 Alleviates L-DOPA-Induced Dyskinesia in the 6-Hydroxydopamine-Lesioned Rat Model of Parkinson's Disease

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L-3,4-dihydroxyphenylalanine (L-DOPA) is the most effective treatment for Parkinson's disease (PD) but long-term use is marred by dyskinesia. Here, we investigated the effects of the highly-selective mGluR2 positive allosteric modulator LY-487, 379 at alleviating and preventing the development of L-DOPA-induced dyskinesia (LID). Rats were rendered parkinsonian by administration of 6-OHDA. In the first set of experiments, rats were primed with L-DOPA to induce axial, limbs and oro-lingual (ALO) abnormal involuntary movements (AIMs), after which L-DOPA was administered, in combination with LY-487,379 (vehicle, 0.1, 1 and 10 mg/kg). In the second set of experiments, rats were administered LY-487,379 (0.1 or 1 mg/kg), started concurrently with L-DOPA for 21 days. After a 2-day washout period, an acute challenge of L-DOPA was administered and ALO AIMs severity was assessed. The effect of LY-487,379 on L-DOPA anti-parkinsonian action was determined by the cylinder test. Acute challenges of LY-487,379 0.1 mg/kg in combination with L-DOPA, significantly diminished the severity of ALO AIMs, by 40% ($P<0.05$), compared to L-DOPA alone. LY-487,379 0.1 mg/kg, when started concurrently with L-DOPA, attenuated the priming process leading to the development of dyskinesia, when compared to L-DOPA alone, by 82% ($P<0.05$). The anti-dyskinetic action of LY-487,379 did not impair L-DOPA anti-parkinsonian activity. These results suggest that selective mGluR2 activation is an effective and promising therapeutic strategy to alleviate the severity, and prevent the development, of dyskinesia.

3-C -83 Role of Neurexin in Amyloid β-induced Synapse Pathology

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Synapse dysfunction and loss are the early characteristics of Alzheimer's disease (AD), whose pathological feature is the excess production of toxic amyloid-β (Aβ)-peptides. Although, many previous researches have shown that soluble Aβ oligomers (AβOs) reduce synapse number, the underlying molecular mechanisms have not been yet well demonstrated. Here we performed Aβ binding screen for cell adhesion proteins with synapse induction ability, called synapse organizers, and identified a novel interaction between neurexins (NRXs) and AβOs. AβOs bind to NRXs via the N-terminal histidine-rich domain (HRD) of β-NRX1/2/3 and alternatively-spliced inserts at splicing site 4 of NRX1/2. In artificial synapse-formation assays, AβOs diminish excitatory presynaptic differentiation induced by NRX-interacting proteins such as neuroligin1/2 (NLG1/2) and the leucine-rich repeat transmembrane protein LRRTM2, while the presynaptic inductions mediated by Protein tyrosine phosphatases (PTPs) were not affected. As a further cellar mechanism, time-lapse imaging revealed that AβO treatment suppresses the surface expression of NRX1β on axons in the HRD-dependent manner. In transgenic mice model with mutated human amyloid precursor protein, synaptic expression of β-NRXs, but not α-NRXs, specifically decreases. In conclusion, our results indicate that AβOs interact with NRXs and that this interaction

inhibits NRXs-mediated presynaptic differentiation by reducing surface expression of axonal β-NRXs. These findings will help to develop new therapeutic strategies targeting to the AβOs-NRXs interaction.

3-C -84 Deciphering the role of hematopoietic stem/progenitor cells highly expressing interleukin-1 receptor in experimental autoimmune encephalomyelitis.

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Hematopoietic stem cells (HSCs) are the main source of the leukocytes and thus possess the capacity of reacting to inflammatory processes by generating the proper cell type that will either promote or resolve inflammation. Our recent experiments have shown that Lin- Sca1+ cKit+ HSCs infiltrate the spinal cord of mice that develop a disease similar to multiple sclerosis (MS), namely experimental autoimmune encephalomyelitis (EAE). Hence, we aim to further characterize this specific subset of HSCs and their role in autoimmunity and MS, especially in regard to interleukin (IL)-1 signaling. To do so, EAE is actively induced by s.c. injections of MOG35-55 in WT mice and mice lacking either IL-1β or IL-1R1. The presence of HSCs or their progeny is monitored and characterized by immunofluorescence staining and by flow cytometry (FC). The Lin- cell population found in the spinal cord of EAE mice expresses high levels of IL-1R1. Based on this high expression of IL-1R1, we were able to locate these cells in the bone marrow, spleen and lymph nodes of naïve and EAE mice. FC analysis of IL-1R1+ Lin- cell populations revealed that these cells are HSCs and early multipotent progenitor cells (MMPs). Intravenous injection of IL-1R1+ HSCs/MMPs during the induction phase of EAE worsened clinical signs of EAE. Furthermore, deficiency in IL-1β or IL-1R1 prevented neuroinflammation and EAE development. This suggests that interfering with IL-1 signaling in HSCs/MMPs might be of great relevance to EAE and MS.

3-C -85 Increased Excitability of Dorsal Root Ganglia Neurons in the Experimental Autoimmune Encephalomyelitis Model of Multiple Sclerosis is Cell Type Specific

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Multiple Sclerosis (MS) is a demyelinating autoimmune disease which leads to motor and sensory dysfunctions. Experimental autoimmune encephalomyelitis (EAE) is an animal model to induce demyelination to mimic MS. As seen in MS, EAE mice show signs of neuropathic pain (mechanical and cold allodynia; Olechowski et al., Pain 141:156, 2009). Although some studies have shown maladaptive changes in the dorsal root ganglia (DRG) of EAE mice, such as an increase in IL-1β and TNFα, contribute to pain onset; no electrophysiological examination of changes in the DRG neurons have been done. To understand how the EAE-induced changes in the DRG cause the onset of neuropathic pain; we compared the excitability of DRG neurons of complete Freund's adjuvant (CFA) control mice, EAE onset mice and EAE mice 7-8 days after disease onset. We found that myelinated DRG neurons (cell body size >28μm) in EAE onset and 7-8d EAE mice fire more action potentials in response to depolarizing current compared to CFA controls. However, there were no differences between control and the EAE mice groups in unmyelinated DRG neurons (cell body size <28μm). Myelinated DRG neurons in EAE onset group had lower rheobase compared to CFA controls but rheobase of myelinated DRG neurons was unchanged. Furthermore, both myelinated and unmyelinated EAE onset DRG neurons showed decreased action potential afterhyperpolarization amplitude. These findings suggest that increased excitability of myelinated DRG neurons may contribute to the onset of signs of neuropathic pain in the EAE mouse model.

3-C -86 A brain-computer interface for communication with an unresponsive wakefulness syndrome patient

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An unresponsive wakefulness syndrome (UWS) patient was assessed by a BCI system to examine whether he is able to communicate. The system works with two models, a) vibro-tactile P300 model with 2 vibrators (VT2); and b) vibro-tactile with 3 vibrators (VT3). In both models, odd-ball paradigms were presented to the patient for two and half minutes, and the patient was instructed to actively count deviant vibro-tactile stimuli. In the second model, there was one vibrator on the left hand of the patient, one on the right hand, and the third one on a neutral midline location. During the testing stage, the patient was asked to count either the stimuli on the left or right hand to produce a corresponding P300 response on the EEG data. The evoked potentials were calculated and statistically analyzed, meanwhile, the EEG data was trained by a classification algorithm to provide an initial measure on the classification rate. Then in the next evaluation stage, the patient was asked by simple questions, and he could answer "YES" by counting the stimuli on the right hand, or answer "NO" by counting the stimuli on the left hand. For both VT2 and VT3 models, the system achieved 100% accuracy during the testing stage when P300 response was generated, and based on this data, the system was calibrated and 20 questions were asked to the patient. 15 were answered correctly, 1 was wrong and 4 were undetermined. The system shows the potential of BCI system for assessing DOC patients and could help us understand if the patient still has some cognitive functions.

3-C -87 Translating the impact of Mindfulness-Based Stress Reduction (MBSR) among breast cancer survivors with chronic neuropathic pain: A preliminary look at structural connectivity of the brain

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Some studies have indicated that Mindfulness Based Stress Reduction (MBSR) can be an effective treatment for neuropathic pain, ameliorating physical and psychosocial symptoms. Such results are promising given that well-established treatment interventions for individuals in this population have proven elusive. There is also evidence that altered structural connectivity of the brain is apparent in this population. The purpose of this study was to determine if, using structural diffusion tensor imaging, MBSR had an effect on structural connectivity of the brain in a sample of women with neuropathic pain after treatment for breast cancer. A total of 20 participants were recruited from cancer centers in Ottawa, Canada forming two groups: MBSR vs.wait-list control. Voxelwise whole-brain analysis of functional anisotropy (FA) data was carried out using Tract-Based Spatial Statistics (TBSS v1.2). Statistical maps were inspected at $p < .05$ corrected for multiple comparisons. Testing protocol was conducted prior to and after an 8-week MBSR intervention No statistically significant group differences were found in global brain functional anisotropy (FA) values between groups at Time 2, or within the MBSR group at Time 1 and Time 2. These results suggest that an MBSR intervention does not improve the negative impact of neuropathic pain on global white matter. Notably, some functional imaging measures in this same cohort reflected significant changes in regions associated with emotional reactivity. Present results may be reflective of limited program duration or intervals between scans.

3-C -88 The contributions of the ventral tegmental area to the expression of antipsychotic-induced dopamine supersensitivity

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Antipsychotics (AP) reduce schizophrenia symptoms by decreasing dopamine (DA) signalling. Paradoxically, chronic AP can produce DA supersensitivity, leading to treatment failure and an increased risk of psychotic relapse. In rats, AP-evoked DA supersensitivity enhances the behavioral effects of DA agonists such as amphetamine (AMPH). The mesocorticolimbic DA system, which originates in the ventral tegmental area (VTA), regulates AMPH-induced behavioral effects. We hypothesized that increasing VTA neuron activity is sufficient to evoke the expression of AP-induced DA supersensitivity. Following 2 weeks of treatment with the AP haloperidol, we evaluated the locomotor effects of an intra-VTA injection of neurotensin or DAMGO, two peptides that enhance DA cell firing and release, and locomotion. AP-treated rats showed potentiated AMPH-induced locomotion relative to controls, indicating DA supersensitivity. However, AP-treated rats had reduced or unchanged neurotensin- or DAMGO-induced locomotion. This indicates that enhancing VTA DA impulse flow is insufficient to evoke AP-induced DA supersensitivity. Thus, activation of non-DA systems, of DA transmission outside of the mesocorticolimbic system and/or of the periphery is necessary. Hence, we evaluated the locomotor effects of systemic GBR12783 (a selective DA uptake inhibitor) or intra-ventricular AMPH following AP treatment. Neither treatment induced a level of locomotion indicative of DA-supersensitivity. This suggests that non-DA systems and the periphery are implicated in AP-evoked DA supersensitivity.

3-C -89 Dissecting the molecular pathway involved in PLK2-mediated α-synuclein selective autophagic degradation

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Accumulation and aggregation of the pre-synaptic protein, α-synuclein (α-syn) plays a key role in the pathogenesis of Parkinson's disease (PD) and other synucleinopathies. Therefore, the decreasing of α-syn protein levels may represent a viable therapeutic strategy for the treatment of PD and related disorders. Recently, we described a novel selective α-syn degradation pathway, catalyzed by the activity of the Polo-like kinase 2 (PLK2), capable of reducing α-syn protein expression and suppressing its toxicity, in living cells and also in vivo. However, the exact cellular and molecular mechanisms underlying this degradation route remain elusive. In this study, we report that the level of α-syn expression can be reduced after being phosphorylated by a certain members of polo-like kinases. Interestingly, PLK2 and PLK3 efficiently phosphorylate α-syn on the residue S129 and enhances its elimination via the macroautophagy pathway. This degradation pathway requires α-syn/PLK2 protein-protein interaction. Moreover, our data demonstrate that this protein complex is ubiquitinated and suggest that this post-translational modification may facilitate its selective recognition by the macroautophagy machinery and a co-degradation of the two proteins. This newly described pathway offers opportunities for the development of efficient therapeutic strategies for PD aiming to reduce α-syn accumulation and toxicity in a specific and selective manner.

3-C -90 The highly-selective metabotropic glutamate receptor 2 positive allosteric modulator LY-487,379 alleviates psychosis-like behaviours and dyskinesia in the MPTP-lesioned marmoset

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Psychosis and dyskinesia undermine the quality of life of 50-95% of patients with advanced Parkinson's Disease (PD). Serotonergic 2A receptor (5-HT2AR) blockade is a validated approach to alleviate both psychosis and dyskinesia, but the effectiveness of this approach is also limited. 5-HT2AR forms a functional hetero-complex with metabotropic glutamate receptor 2 (mGluR2) involved in psychotic symptoms and hallucinations. Our objective is to investigate the effect of activation of mGluR2 on L-3,4-dihydroxyphenylalanine (L-DOPA)-induced psychosis-like behaviours (PLBs) and dyskinesia in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned marmoset model of PD. Six common marmosets were rendered parkinsonian by MPTP administration. Dyskinesia and PLBs were induced by chronic administration of L-DOPA. The highly-selective mGluR2 positive allosteric modulator LY-487,379 (vehicle, 0.1, 1 and 10 mg/kg) was then administered in combination with L-DOPA and its effects on each of dyskinesia, PLBs and parkinsonism were assessed. LY-487,379 1 and 10 mg/kg significantly alleviated PLBs (by 35% and 42% respectively, $P<0.05$), when compared to vehicle. LY-487,379 1 and 10 mg/kg also significantly reduced the severity of dyskinesia (by 46% and 53% respectively, $P < 0.05$). LY-487,379 also significantly improved the quality of on-time. Importantly, LY-487,379 did not hinder with L-DOPA anti-parkinsonian action. Selective mGluR2 activation stands as a new and promising approach to alleviate both PD psychosis and dyskinesia without negative impact on parkinsonian symptoms.

3-C -91 Recording Event-Related Potentials from Unresponsive Populations: Identifying Best Practices and Implications for the Study of Consciousness

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Traditionally, long-latency event-related potentials (ERPs) such as the P3b and N400 have been considered markers of consciousness. However, recent studies have drawn this relationship into question by demonstrating the existence of these ERPs in unconscious individuals and failing to detect them in conscious individuals. A consistent limitation to these studies is a failure to consider the multivariate factors that affect ERP elicitation and detection in unresponsive populations. Reviewing and assessing data collected from both healthy controls and unresponsive patients over several years, we identify and discuss four factors that influence the presence and morphology of the P3b and N400 waveforms that are of particular importance to this population. We present contrasts within each condition and establish experimental guidelines pertaining to each result. We recommend that: 1) the strongest paradigms should be used to elicit ERPs in unresponsive populations 2) interpretation of ERP results should account for participant age 3) subjects should always be instructed to pay attention to ERP stimuli and tasks 4) speed of stimulus presentation should be slower in unresponsive populations. Designing ERP studies for eliciting and recording ERPs in unresponsive individuals must be carried out with exquisite care. The application of these best practices will minimize result interpretation ambiguity, increase confidence in conclusions, and advance the understanding of the relationship between long-latency ERPs and states of consciousness.

3-C -92 Implementation of a Novel Imaging Technique to the Study of Post-Stroke Myelin Pathophysiology

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Ischemic stroke induces widespread pathophysiology including axonal degeneration and demyelination. While demyelination is thought to contribute to the functional impairment that follows stroke, the

temporal profile of de- and re-myelination following stroke is not well described, and their relation to cortical network impairment and recovery is not defined. Here, we used a novel in vivo imaging approach (ScoRe microscopy) to visualize myelin changes in the peri-infarct cortex of mice for 6 weeks following targeted photothrombosis of the forelimb somatosensory cortex. De- and re-myelination were compared to functional remapping of the fore- and hind-limb somatosensory representations visualized via longitudinal optical imaging. Demyelination was evident and severe in superficial cortical layers proximal and distal to the ischemic core by 1 day post-stroke, with significant recovery of intact myelinated structures visible by day 7 in the distal regions and by day 14 in the proximal regions. Remyelination was highly correlated with functional remapping of the forelimb and hindlimb sensory cortices, confirming a role for myelin integrity in network function and recover following stroke. Future studies will focus on the use of SCoRE microscopy and functional imaging to evaluate controlled manipulations of myelin integrity and better define the role of myelin in stroke recovery.

3-C -93 Cerebellar pathophysiology and its treatment in spinocerebellar ataxia type 6 mice

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Spinocerebellar ataxia type 6 (SCA6) is a mid-life onset neurodegenerative disease that affects motor control and gait, and has no known treatment. SCA6 is caused by a CAG repeat expansion in the CACNA1A gene encoding the P/Q-type Ca2+ channel α1A subunit that is enriched in cerebellar Purkinje cells. Using a knock-in mouse model that harbors an 84-CAG repeat, we found that SCA684Q/+ Purkinje cells exhibit reduced precision of spontaneous spike timing (measured by the coefficient of variation, CV, of interspike intervals), compared to WT cells ($P<0.005$) without any significant change in firing rate ($P=0.71$) when motor deficits are observed at 19 months. Likewise, at 7 months when motor deficits are observed in SCA684Q/84Q mice, Purkinje cells exhibit reduced firing rate (firing rate: 56±4 Hz, n=27 cells) and a reduced precision of spike timing (CV: 0.14±0.01 ms, n=27 cells) compared to wildtype (WT) (firing rate: 72±6 Hz, n=30 cells, $P<0.05$; CV: 0.09±0.01 ms, n=30 cells, $P<0.001$). Using chronic oral administration of the potassium channel blocker 4-aminopyridine (4-AP), we partially rescued motor deficits in 7-month-old SCA684Q/84Q mice (Rotarod performance after 2 weeks of 4-AP, SCA684Q/84Q: 71.50±1.83 s, n=9 mice; SCA684Q/84Q+4-AP: 119.16±1.15 s, n=11 mice, $P<0.0001$). 4-AP also restored spike timing precision in SCA684Q/84Q Purkinje cells to WT levels (CV: 0.10 ± 0.01, n=11 cells, $P < 0.01$) without affecting firing rate ($P=0.15$). These results provide a novel therapeutic approach for the treatment of motor deficits in SCA6.

3-C -94 Motor deficits in a zebrafish model of Parkinson's disease

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Parkinson's disease is characterized by the loss of dopaminergic (DA) neurons in the substantia nigra. These DA neurons project to various nuclei of the basal ganglia to shape motor control. Parkinson's disease (PD) patients exhibit motor symptoms that include bradykinesia, hypokinesia, and impaired eye movements. The zebrafish is an intriguing model for PD. There is a basal ganglia homolog in the zebrafish and the striatum homolog receives strong DA innervation. Therefore, zebrafish could be a valid model to study motor dysfunction in PD. In order to validate zebrafish as a model of PD, we sought to characterize the motor symptoms of a DA-depleted strain of fish. In this study we use behavioral tests on larval zebrafish to test the ability of fish to generate fast swimming events and saccadic eye movements. To generate a PD model of zebrafish with depleted levels of DA, Tg(dat:CFP-NTR) fish are

raised in a metronidazole (MTZ) infused environment. MTZ is converted by NTR into a cytotoxic product that leads to the selective loss of DA neurons. DA-depleted fish exhibit longer periods of inactivity and swim smaller distances during their fast movements than their DMSO-treated counterparts. We found that DA-depleted fish have lower numbers of saccades in the optokinetic response test. Lastly, an analysis of the power spectrum of body bends during swimming suggests differences in the kinematics of swimming. These findings suggest that the loss of DA in zebrafish causes disturbances that are homologous to the bradykinesia and hypokinesia seen in patients with PD.

3-C -95 Spatial Rearrangements of Astrocytes and Microglia in the Ageing Down Syndrome Brain

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Alzheimer 's disease (AD) neuropathology has been shown to develop in a high proportion of DS adults. Like in AD, DS brain pathology includes synaptic loss, neurodegeneration, beta amyloid (1-42) (Aβ) deposition, tauopathy, neurofibrillary tangles, glial reactivity, and neuroinflammation. To better understand brain pathology in DS and AD we pioneered a labeling and imaging method which enables multi-channel 3D light microscopic analysis of neurons and glial cells in long term fixed DS and AD tissue samples. Using this method we investigated the reorganization of activated microglia and reactive astrocytes near sites of neuropathology such as Aβ plaques and neurofibrillary tangles in DS. Detailed quantifications show extensive glial remodeling in DS and the assembly of specialized structures that we term Reactive Glial Nets (RGNs) around distinct Aβ types. Interestingly, we also show progressive changes in the interactions of microglia and astrocytes with Aβ plaques with age in both the frontal cortex and in the hippocampus. Thus, glial cells actively participate in brain pathology in DS. To study molecular mechanisms involved in glial-mediated pathology in DS, we have developed an in vitro model using Induced pluripotent stem cells (iPSCs) reprogrammed from fibroblasts of 3 DS individuals as well as 3 control individuals. We are currently developing protocols to investigate the contributions astrocytes to neuronal pathology. In the future, this IPSC model will provide a platform for modifying both glial and neuronal pathways that contribute to cellular dysfunction.

3-C -96 The Search for Effective Correction- Systemic Hexosaminidase Hybrid Gene Therapy on Neonatal and Adult Sandhoff Mice

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GM2 Gangliosidosis are neurodegenerative disorders caused by a deficiency of Hexosaminidase A enzyme (HexA). HexA (α- and β- subunits) is the only enzyme able to catabolize GM2 gangliosides (GM2); in the central nervous system the deficiency of HexA leads to GM2 accumulation, which causes neuronal death. In our previous works, a hybrid subunit was constructed to replace HexA by integrating the catalytic properties of the α-subunit, and the stabilization sites of the β-subunit. The hybrid μ-subunit, coded by HEXM, homodimerizes to form HexM, which catabolize GM2. In the current study, the HEXM was packaged into adeno-associated virus 9 (AAV9) and was given intravenously to adult and neonatal (NEO) Sandhoff (SD) mice to assess the efficiency of systematic treatments at different ages of administration. We injected 2.5E14vg/kg dose in NEO mice. In the adult HEXM treated group, we used two doses, 5E14vg/kg (high dose, HD) and 1.25E14vg/kg (medium dose, MD). We hypothesized that the HEXM treatment would significantly improve survival, locomotion, and biochemical. Although untreated SD mice reach humane end-point at 16 weeks of age, the NEO, HD, and MD treated SD mice survived

significantly longer, an average of 44.7, 58.8, and 40.6 weeks, respectively. Biochemical data shows an increase in enzyme activity and a decrease in GM2 storage in the HEXM treated mice. Preliminary behavioural data shows HEXM treated mice perform better than controls. Results from this study provide solid proof of the corrective abilities of AAV9/HEXM at both the neonatal- and adult-age administrations.

3-C -97 Effects of Memogain® on Phosphorylated Tau and Neurogenesis in a Rodent Model of Basal Forebrain Cholinergic Cell Loss

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Memogain® (GLN-1062) is a novel pro-drug of the cholinesterase inhibitor, galantamine, currently used for the treatment of mild to moderate Alzheimer's disease. Memogain enters the brain much more readily than its parent compound, galantamine, and remains inactive until it is enzymatically cleaved in the brain. By improving the efficiency and safety of galantamine delivery to the brain, it becomes possible to explore other, potentially disease-modifying, actions of this natural alkaloid. Galantamine also acts as a positive allosteric modulator of the α7 nicotinic receptor, activation of which has been found to enhance both cell proliferation and survival. Activity at α7 nicotinic receptors has also been shown to regulate tau phosphorylation. Tau is a microtubule associated protein that has several functions under normal physiological conditions such as microtubule stabilization, primarily regulated through phosphorylation. In the brain, tau is predominantly found in neuronal axons and somatodendritic compartments. Through its involvement in microtubule stability and dynamic instability, tau influences the morphology and axonal growth of new neurons. Specifically, phosphorylated tau (p-tau) is involved in neurogenesis by facilitating the migration of new and developing hippocampal neurons from the subgranular zone to the dentate gyrus and may also affect the rate of differentiation for those neurons. Here, we report on the effects of Memogain treatment on tau phosphorylation and neurogenesis in the adult rat brain following the loss of basal forebrain cholinergic neurons.

3-C -98 Investigating pupil dynamics in patients with neurodegenerative diseases

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Brain loss in neurodegenerative diseases lead to impairments in various autonomic, motor, and cognitive functions. An easy-to-measure method that is increasingly used in clinical investigations to assess cognitive function is pupillometry. Pupil size is modulated by converging bottom-up sensory and top-down cognitive signals, as well as arousal and global luminance. Furthermore, the circuit for pupil control is suggested to be linked to the saccade generation system. We hypothesize that disruptions in neural circuitry due to neurodegeneration or brain injury can affect pupil control and its relationship to the saccade system. Here, we examined pupil dynamics in 6 neurodegenerative diseases (Alzheimer's disease, mild cognitive impairment, Parkinson's disease, amyotrophic lateral sclerosis, frontotemporal dementia, vascular cognitive impairment) and hypothesized that components of the pupil response should be altered due to neurodegeneration. Pupil size and eye position were recorded while subjects performed the interleaved pro-/anti-saccade task. The pupil constricted shortly after the presentation of the fixation cue following by dilation. Analysis revealed distinct differences between patient groups and age-matched controls in their pupil dynamics, including measurements of pupil constriction and dilation.

The results demonstrated changes in pupil dynamics linked to neurodegeneration, showing that pupil measurements have the potential to serve as a behavioural biomarker for diagnosis of neurodegenerative diseases and tracking disease progression.

3-C-99 Age-related changes in hippocampal subfields and white matter across childhood and adolescence

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The hippocampus is critically important for episodic memory and spatial navigation. Importantly, this region is comprised of cytoarchitecturally distinct subfields that display unique maturational trajectories. These maturational changes are believed to influence episodic memory development. While age-related changes in hippocampal subfields have recently been characterized, little is known about the pattern of age-related changes in hippocampal white matter (i.e.: alveus, fimbria, fornix) relative to hippocampal subfields. Here, we examined hippocampal subfield and white matter volumes in forty-nine typically developing children and adolescents (age range = 5.2 to 17.5). The hippocampus was automatically segmented into right and left subfields (i.e.: Cornus Ammonis (CA) 1, CA2-3, dentate gyrus (DG)-CA4, stratum radiatum-lacunosum-moleculare and subiculum), and white matter (alveus, fimbria, fornix) on T1-weighted magnetic resonance images. Age-related changes in each region of interest were examined using quadratic and linear fits, and all analyses were corrected for multiple comparisons. Analyses revealed significant linear age-related volume increases in the right DG-CA4, right fimbria and right fornix, suggesting that these regions continue to undergo volumetric changes into adolescence. These findings may provide insight into the structural changes contributing to episodic memory development. Further, given hippocampal subfields and white matter are altered in neurodevelopmental disorders, our findings may aid in identifying patterns of abnormal hippocampal maturation.

3-C -100 Metabolic stress in glaucoma engages early activation of the energy biosensor AMPK leading to neuronal dysfunction

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Purpose: The adenosine monophosphate-activated protein kinase (AMPK) is a regulator of metabolic homeostasis that becomes active at the onset of energy deficits. AMPK is a potent inhibitor of the mammalian target of rapamycin complex 1 (mTORC1), which we showed is essential for the maintenance of retinal ganglion cell (RGC) dendrites, synapses, and survival. Here, we tested the hypothesis that AMPK is an early mediator of metabolic stress in glaucoma. Methods: Unilateral elevation of intraocular pressure was induced by injection of magnetic microbeads. AMPK was blocked by administration of siRNA or compound C (CC). RGC dendrites, soma and axons were analyzed in Thy1-YFP mice. RGC function was examined by anterograde axonal transport. Retinas from glaucoma patients were analyzed for expression of active AMPK. Results: Ocular hypertension triggered rapid upregulation of AMPK activity in RGCs concomitant with loss of mTORC1 function. AMPK inhibition with CC or siRNA effectively restored mTORC1 activity and promoted an increase in total dendritic length, and complexity relative to control. Attenuation of AMPK activity led to robust RGC soma and axon survival. Importantly, blockade of AMPK activity effectively restored anterograde axonal transport. Lastly, RGC-specific upregulation of AMPK activity was detected in human glaucomatous retinas relative to age-matched

controls. Conclusions: Metabolic stress in glaucoma involves AMPK activation and mTORC1 inhibition promoting early RGC dendritic pathology, dysfunction and neurodegeneration.

3-C -101 The Effect of a Novel IDO Inhibitor on the Behaviour and Neuropathology of the 3xTG Mouse Model of Alzheimer's Disease

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The kynurenine pathway is one of the main pathways by which tryptophan is metabolized. While the final product is nicotinamide adenine dinucleotide (NAD), multiple by-products are also produced, including kynurenic acid, which is neuroprotective, 3-hydroxykynurenine, which is involved in oxidative stress, and quinolinic acid, which has neurotoxic properties and is involved in tau phosphorylation. These by-products have been shown to be associated with Alzheimer's disease (AD) in a bi-directional manner. In this study we tested the effect of ST-27, a novel CNS penetrant indoleamine 2,3-dioxygenase (IDO1) inhibitor, which is the first and rate limiting enzyme in the kynurenine pathway. We evaluated the behaviour and neuropathology of the 3xTg-AD mouse model of AD, which show extracellular amyloid beta plaque pathology and cognitive deficits at 6 months of age. We dosed male and female 3xTg-AD mice with ST-27 from two to six months of age. At six months of age we tested their cognitive, motor, and emotional function with the elevated plus maze, Barnes maze, forced swim, tail suspension, rotarod and trace fear-conditioning tasks, and assessed their frailty levels. Then we quantified IDO1, quinolinic acid, kynurenic acid, tryptophan, kynurenine, amyloid beta, phosphorylated tau and the immune activation marker TXNIP in the brain. To our knowledge, this is the first study done on the 3xTg-AD mice using an IDO inhibitor, which measures both behavioural and neuropathological changes.

3-C -102 Regeneration of retinal ganglion cell dendrites and synapses after axonal injury: the role of insulin on regrowth and reconnection

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Purpose: Evidence indicates that axonal injury triggers early dendrite alterations. We asked whether dendrites can be stimulated to regenerate once they have retracted and we investigated the role of insulin, an activator of the mammalian target of rapamycin (mTOR). Methods: Optic nerve axotomy was performed and insulin was administered daily 3 days after injury, when dendrites have retracted. Rapamycin, an inhibitor of mTOR complex 1 (mTORC1) and siRNA against rictor, an essential component of mTORC2 were used. CMV:tdTomato and CMV:PSD95-YFP were biolistically delivered to visualize RGC glutamatergic postsynaptic sites. 7 days post-lesion, RGC dendritic trees and synapses were 3D-reconstructed and analyzed. RGC survival was assessed by quantification of RBPMS-labeled cells. Results: Our data show that insulin promotes remarkable dendrite regeneration, restoring dendritic length, field area, and complexity to values found in naïve retinas. Insulin induced regeneration of excitatory synapses in OFF-transient, OFF- and ON-sustained RGCs. Inhibition of mTORC1 resulted in specific loss of dendritic complexity. In contrast, blockade of mTORC2 resulted in reduced length and field area. Insulin stimulated RGC survival through both complexes. Conclusions: 1) insulin promotes RGC dendrites and likely synapse regeneration, 2) both mTOR complexes are required, mTORC1 controlling complexity and mTORC2 governing elongation, 3) insulin stimulates survival through TORC1/2 activation. Strategies to regenerate dendrites and synapses may have implications to restore vision in glaucoma.

3-C -103 ¬IL-15 enhances pro inflammatory T cell responses in multiple sclerosis and experimental autoimmune encephalomyelitis

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Although it is well established that the immune system participates in tissue destruction in multiple sclerosis (MS), the contribution of immune mediators to injury remains to be defined. Our group has identified interleukin-15 (IL-15) as a key factor in MS pathobiology. We hypothesize that IL-15 contributes to immune-mediated damage in MS and constitutes a valid therapeutic target. We measured elevated IL-15 mRNA levels in the CNS of EAE mice at the disease peak. The percentage of T cells expressing IL-15 receptor chain (CD122) is increased in the CNS and in periphery during EAE development. Moreover, a higher proportion of CNS infiltrated CD4 T cells bearing CD122 displays a pro-inflammatory profile as illustrated by GMCSF/KLRG1/CD44 expression. In addition, we observed aggravated clinical score and higher number of CNS-infiltrating T cells following peripheral injections of IL-15. Our data suggest that elevated peripheral IL-15 levels during EAE are deleterious. Finally we compared the impact of IL-15 on human T cell polarization and intracellular signaling (pSTAT3/5) in cells isolated from MS patients and healthy controls (HC). We found that IL-15 enhances the polarization of CD8 T cells as determined by IFNγ /TNF production; this cytokine also triggers stronger signaling in human memory CD8 and CD4 T cells than in their naïve counterparts . Altogether, our results indicate that IL-15 enhances proinflammatory T cell responses in human and augments murine EAE severity. Therefore, this cytokine represents a potential valid target in MS pathobiology.

3-C -104 Live imaging of retinal pericytes: evidence for early calcium uptake, capillary constriction and vascular dysregulation in ocular hypertension glaucoma

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[1]University of Montreal

Purpose: Pericytes are contractile cells that wrap along the walls of capillaries, playing a crucial role in the regulation of capillary diameter. The contribution of pericytes to microvascular deficits in glaucoma is currently unknown. Here, we used 2-photon excitation microscopy for monitoring of retinal pericytes and capillaries in a mouse glaucoma model. Methods: Ocular hypertension was induced by injection of magnetic microbeads into the anterior chamber of mice expressing red fluorescent protein selectively in pericytes (NG2-DsRed). Multiphoton imaging through the sclera of live NG2-DsRed mice was used to visualize pericytes and capillary diameter at 1, 2 and 3 weeks after glaucoma induction. In vivo fluctuations in pericyte intracellular calcium were monitored with the calcium indicator Fluo-4. Ex vivo stereological analysis of retinal tissue prior to and after injection of microbeads was used to confirm our in vivo findings. Results: Live 2-photon imaging of NG2-DsRed retinas demonstrated that ocular hypertension induced progressive accumulation of intracellular calcium in pericytes, which correlated directly with the narrowing of capillaries in the vascular plexuses (capillary diameter: naïve control=4.7±0.1µm, glaucoma=4.0±0.1µm, n=5-6 mice/group, Student?s t-test $p<0.05$) after induction of ocular hypertension. Conclusions: Ocular hypertension triggers rapid intracellular calcium increase in retinal pericytes leading to substantial capillary constriction. This study identifies retinal pericytes as important mediators of early microvascular dysfunction in glaucoma.

3-C -106 INCREASING AXONAL ARBORIZATION SIZE OF DOPAMINE NEURONS TO PRODUCE A BETTER MOUSE MODEL OF PARKINSON?S DISEASE

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[1]Université de Montréal

In Parkinson's disease, dopamine (DA) neurons of the substantia nigra (SNc) are particularly vulnerable to degeneration. Arborization size of a single DA neuron in humans is hypothesized to be much larger than in rodents, which could account for the apparently higher resilience of rodent DA neurons. Partial lesion of DA neurons in the SNc induces a compensatory axonal sprouting of surviving neurons. Our hypothesis is that a partial lesion in the neonate mouse SNc will result in adults with DA neurons that have a larger axonal arborization and increased vulnerability. These compensating DA neurons would thus exhibit increased vulnerability to toxins and potentially undergo age-dependent PD-like neurodegeneration. We have optimized a protocol in neonates (P5) using a unilateral injection of the neurotoxin 6-hydroxydopamine and inducing an approximate 50% lesion of SNc DA neurons. At P90, axonal arborization size of surviving DA neurons will be quantified via intranigral injection of a green fluorescent protein virus. The vulnerability of compensating DA neurons will then be compared to control DA neurons by injecting mice bilaterally with a virus that induces overexpression of alpha-synuclein. Our initial results have confirmed axonal sprouting of surviving SNc DA neurons at early time points post-lesion. Preliminary data is currently being analyzed to establish whether the vulnerability of surviving adult SNc DA neurons is increased. This strategy may allow us to obtain a novel mouse model of PD more representative of the high vulnerability of DA neurons in humans.

3-C -107 The neurotoxic effects of soluble amyloid-beta oligomers on memory processing and sleep at the onset of AD

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In Alzheimer?s disease (AD), synapse loss and ensuing neurodegeneration are the best predictors of memory impairments. Soluble amyloid-beta oligomers (Aâo) start to accumulate in the human brain 10 to 15 years before clinical symptoms, and correlate with cognitive decline in AD models and humans. Memory deficits in mild cognitive impairment (MCI) and early AD was shown to be accompanied by poor sleep quality, difficulty initiating sleep, insomnia, and early morning wakening. Although recent ground-breaking discoveries have shown the critical impact of sleep on the regulation of Aâo level in the brain, the interaction existing between soluble Aâo and sleep loss to induce memory impairments at the onset of AD still need to be determined. To study the bidirectional relationship of sleep and Aâ in the early stages of AD, we took advantage of our novel AD animal model in which repeated Aâo injections mimic the synaptic and neuronal loss observed in early AD. We observed that hippocampal accumulation of Aâo was associated with progressive and marked cell death. Electroencephalography (EEG) measurements were also done on these animals to analyze various oscillatory activities (delta, theta, sigma, alpha, and gamma waves) during rapid eye movement (REM) sleep and non-REM (NREM) sleep as well as in awake AD animals. The results obtained so far support the notion that soluble Aâo might have a deleterious impact on memory and sleep hallmarks affected in AD.

3-C -108 Altered lipid profile associated with myelin degeneration in the aging brain

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Aging decreases both the stability of myelin and the efficiency of its repair. In the central nervous system (CNS), oligodendrocytes (OLs) continue de novo myelination of cortical white matter (WM) into

adulthood and volume peaks between 40-50 years of age. WM degeneration has been shown to correlate with a decline in cognitive function, particularly in the anterior corpus callosum (CC). However, little is known about the molecular and biochemical changes in the myelin sheath during aging. A reduction in the number of OL lineage cells and myelin gene expression is observed in mice ≥12 months [Doucette et al. 2010], which corresponds to the human age when WM peaks (~40y). Ultrastructural analysis indicates that this is associated with increased splitting of the compact myelin layers and an accumulation of unmyelinated axons in the rostral CC. Novel fourier transform infrared spectroscopy (FTIR) imaging of sagittal brain sections from aging mice shows a decrease in total lipid and protein content of the WM, with some lipid peaks more impacted than others. Of particular interest is a decrease in the lipid carbonyl ester band and the appearance of carbonyl peaks characteristic for byproducts of lipid peroxidation. These changes were more predominant in the genu of the CC. Thus, age-related structural changes in the myelin sheath correspond to distinct biochemical changes in WM. These observations support the hypothesis that myelin tracts associated with the prefrontal cortex are more susceptible to oxidative damage during aging.

3-C -109 Early mitochondrial fragmentation in retinal endothelial cells and vascular dysfunction in ocular hypertension glaucoma

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Early metabolic stress in retinal endothelial cells is predicted to have harmful effects on the integrity of the neurovascular unit and might compromise vascular homeostasis. We hypothesized that ocular hypertension (OHT) triggers early mitochondrial alterations in endothelial cells impairing the integrity of the blood-retinal-barrier (BRB). OHT was induced by injecting magnetic microbeads into the anterior chamber of EndoMito-EGFP mice. Mitochondrial volume, and the number of mitochondrial components from glaucomatous and control retinas were 3D-reconstructed and quantified using Imaris. Dynamin-related protein (DRP-1), mitofusin-2 (MFN-2) and optic atrophy-1 (OPA-1) were assessed by western blot. Mitochondrial structure was evaluated by transmission electron microscopy (TEM) and oxygen consumption rate was monitored by Seahorse analysis. BRB integrity was quantified using Evans blue. Our data show a decrease in total endothelial cell mitochondrial volume at two and three weeks after OHT induction relative to naïve retinas. Frequency distribution showed an increase of smaller mitochondria (<0.5 μm^3) in endothelial cells from glaucomatous retinas. DRP-1 upregulation was found in hypertensive retinas compared to naïve controls, while MFN-2 and OPA-1 remained unchanged. Alterations in the mitochondria was confirmed by TEM, and were accompanied by 2-fold reduction in the oxygen consumption rate and 2.6-fold increase in BRB leakage in glaucoma relative to controls. OHT triggers early alterations in endothelial cell mitochondria leading to vascular dysfunction in glaucoma.

3-C -110 Function of the Syngap1/mTOR pathway in GABAergic cells and cognitive development.

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De novo mutation in SYNGAP1 cause intellectual deficiency, generalized epilepsy and autism spectrum disorder.SYNGAP1 codes for a Ras-GAP protein produced in excitatory and inhibitory neurons.Syngap1 haploinsufficiency restricted to GABAergic cells alters the development and function of the inhibitory circuitry and causes cognitive deficits in mice.The aim of this study is to understand the molecular

mechanism underlying Syngap1 function for the development and function of the GABAergic circuitry.Our hypothesis is that Syngap1 haploinsufficiency causes mTOR hyperactivation in GABAergic cells, therefore altering synapses formation and inducing cognitive deficits.Cued and contextual fear conditioning was assessed in Syngap1flox/+;Tg(Nkx2.1-cre) mice.Co-labelling immunohistochemistries were performed, before (basal level) and after fear conditioning, using antibodies against the phosphorylated form of S6 (pS6), a marker of mTOR activation, and parvalbumin (PV), a marker of a subpopulation of GABAergic neurons.The pS6 marker intensity was measured in the amygdala (AMG) and the prefrontal cortex (PFC).We report that Syngap1flox/+;Tg(Nkx2.1-cre) mice show impaired contextual and cued fear learning. These mice display increased pS6 expression in PV-interneurons compared to excitatory neurons in the AMG and PFC before and after fear conditioning. Syngap1 haploinsufficiency restricted to GABAergic cells induces mTOR hyperactivation and impairs contextual and cued fear learning.We plan to determine whether the administration of mTOR inhibitors can rescue these cognitive deficits.

3-C -111 Carotid stiffness impairs cerebral blood flow regulation and blood-brain-barrier function leading to cognitive deficits

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Epidemiological studies have long linked large artery stiffness to cognitive decline and dementia; however the mechanisms of brain damage induced by arterial stiffness remain unknown. Considering that proper brain perfusion is vital to maintain the high metabolic demand of neurons and cerebral homeostasis, we investigated whether arterial stiffness, independently of age or blood pressure, is sufficient to impair cerebral blood flow (CBF), blood-brain-barrier (BBB) function and cognition. We used a new mouse model of arterial stiffness based on carotid calcification, specifically developed for the study of its effects on the brain. At 2 weeks post-calcification, arterial stiffness significantly attenuated resting CBF in the hippocampus, entorhinal cortex and thalamus, determined by autoradiography ($P<0.05$). Arterial stiffness equally diminished CBF responses to whisker stimulation and to acetylcholine, examined by laser-Doppler flowmetry ($P<0.05$). At this time point, no cognitive deficits were observed. Instead, at 3 weeks post-calcification, memory deficits in the Morris water maze appeared ($P<0.05$). In line with this, carotid stiffness also led to a significant increase in sodium fluorescein uptake in the hippocampus, suggesting a compromise in BBB function ($P<0.05$). Based on these findings we propose that treating arterial stiffness could offer a new paradigm to protect the brain in populations where vascular stiffness is prominent, such as the elderly and hypertensives.

3-C -113 Characterization of new ALS models generated using CRISPR/Cas9

Constantin Bretonneau[1], Alex Parker[1]
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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by a progressive degeneration of upper and lower motor neurons. The majority of ALS cases are sporadic but approximately 10% of cases have a familial origin. Among the genes identified are transactive response DNA Binding Protein 43 (TARDBP) and Fused in Sarcoma (FUS) that account for 5% of familial cases. So, there is an unmet need to develop new animals models to better represent the vast genetic spectrum of this disease. In our laboratory, we use Caenorhabditis elegans as a powerful genetic model to study the cellular and molecular changes that lead to a diseased state. Previously, we have made transgenic worms expressing human mutant and wild-type FUS and TDP-43 in motor neurons, resulting in a

progressive paralysis and neurodegeneration. However, these models are overexpressing the transgenes and may not properly recapitulate human pathology. With the development of CRISPR/Cas9 techniques, we have generated new ALS models by creating point mutations mimicking human disease-causing mutations in the C. elegans orthologue of FUS (fust-1) and TDP-43 (tdp-1). Our goal is to fully characterize these new models and determine if they can recapitulate key aspects of the disease at physiological expression levels. These models would provide better disease relevance and would open the possibility to generate new CRISPR/Cas9 models for other ALS-causing genes.

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3-C -114 Beyond Amyloid - Manipulating metabolism as a potential therapy for Alzheimer's Disease

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A key pathological feature of Alzheimer's disease (AD) is the accumulation of extracellular deposits of amyloid beta (Aß) peptide within the brains of affected individuals. However, 40% of the elderly have pronounced Aß deposition within their brains, yet show no symptoms of dementia, indicating that some cells are resistant to Aß toxicity. Several studies suggest CNS cells that are resistant to Aß toxicity display a metabolic shift from mitochondrial-dependent oxidative phosphorylation (OXPHOS) to aerobic glycolysis for their energy needs. Expression & activation of the adaptor protein p66SHC can shift the cellular metabolic state from OXPHOS to aerobic glycolysis. Hence, we propose that the expression & activation of p66SHC in CNS 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. Changes in mitochondrial electron transport chain (ETC) activity and ROS levels were also measured. Overexpression of p66SHC repressed glycolytic enzyme expression and increased mitochondrial ETC activity and ROS levels. The opposite effect was observed when endogenous p66SHC expression was knocked down. Activation of p66SHC increased sensitivity to Aß toxicity. Our findings indicate that expression and activation of p66SHC

renders CNS cells more sensitive to Aß toxicity by promoting mitochondrial OXPHOS while repressing aerobic glycolysis. Thus, p66SHC may represent a potential therapeutical target for AD.

3-C -115 Investigation of the axonal regeneration potential of the DLK-1 pathway in C. elegans models of amyotrophic lateral sclerosis and Huntington's disease

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Neuronal communication with the local environment is heavily dependent on the axonal structure, and intact axonal projections and terminals are essential to a functioning neuronal network. In many neurodegenerative diseases, the axon is the first structure to degenerate, causing impaired neuronal signaling that can initiate neuronal dysfunction. A novel approach to maintain normal axonal structure consists of stimulating axonal regeneration, which allows an organism to repair damage and to rebuild neuronal connections. A candidate to regulate the axonal regeneration is the evolutionarily conserved dlk-1 gene, whose upregulation has been shown to increase axonal repair after mechanical injury in Caenorhabditis elegans. In this study, we are investigating if an upregulated DLK-1 pathway can also repair axonal damage observed in vivo in a neurodegeneration context. We have used C. elegans models of amyotrophic lateral sclerosis and Huntington's disease, both of which recapitulate some early stages of disease progression including axonal degeneration, and have tested the effects of pharmacological or genetic inhibition on negative regulators of the DLK-1 pathway. Our preliminary data supports the hypothesis that stimulating DLK-1 can be a tool to reduce axonal damage in models of neurodegenerative diseases.

3-C -116 Upregulation of low affinity state dopamine D3 receptors in normal aged and Parkinson disease with dementia brains

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The dopamine D1, D2, D3 receptors, vesicular monoamine transporter type-2 (VMAT2), and dopamine transporter (DAT) densities were measured in aged and Parkinson disease (PD) with dementia brains by quantitative autoradiography. The density of D1 receptors, VMAT2, and DAT was measured using [3H]SCH23390, [3H]dihydrotetrabenazine, and [3H]Win35428, respectively. The density of D2 and D3 receptors was calculated using the D3 selective radioligand, [3H]WC-10 and the D2-preferring radioligand [3H]raclopride using a mathematical model described previously. Additional quantitative autoradiography studies using a dopamine D3 receptor agonist [3H]7-OH-DPAT were also conducted in the same subjects and the high and low affinity state dopamine D3 receptor densities were determined using a mathematical model. Dopamine D1, D2, and D3 receptors are extensively distributed throughout striatum; the highest density of D3 receptors occurred in the nucleus accumbens (NAc). There were no significant changes in the dopamine D1 and D2 receptor densities in PD with dementia striatum and substantia nigra (SN) compared to normal aged cases. VMAT2 and DAT densities were reduced in these brain regions of PD with dementia, however the DAT was significantly decreased in putamen and VMAT2 decreased in the NAc and SN. As expected, decreased dopamine pre-synaptic markers confirms neuronal loss in the substantia nigra pars compacta (SNpc) in these PD with dementia cases, while increased D3 low affinity state receptors in striatal regions may represent a compensatory regulation upon dopaminergic denervation.

3-C -117 Cerebrovascular Safety of Sulfonylureas: The role of KATP Channels in neuroprotection and stroke risk in treatments of type 2 diabetes

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Introduction: Diabetes mellitus (DM) increases stroke risk significantly. Sulfonylureas are the most commonly used anti-diabetics. Sulfonylureas block KATP channels in pancreatic beta cells triggering insulin release. This is problematic as KATP channels demonstrate neuroprotection against ischemia. Few studies have addressed stroke risk associated with different DM treatments. Thus, we investigated the role of KATP channels in neuroprotection and stroke risk associated with DM treatment and KATP blocker sulfonylurea. Methods: To determine DM effect on stroke outcome, streptozotocin (STZ) was injected and middle cerebral artery occlusion (MCAO) performed. Role of KATP channel in neuroprotection was revealed by KATP agonist and antagonist in vitro (oxygen glucose deprivation, neuron cultures) and in in vivo model (MCAO, 6 week old male C57BL/6J) of ischemic stroke. Meta-analysis was performed and multivariate logistic regression was used to determine stroke occurrence and sulfonylurea use. Results: STZ-induced diabetic mice displayed larger infarct, more stroke related proteins and behavioral deficit post-MCAO. Tolbutamide increased OGD-induced cell death and MCAO-induced infarct and neurobehavioral deficits while diazoxide conferred neuroprotection. Meta-analysis showed higher stroke morbidity ratio in T2DM patients using sulfonylureas. Discussion: Sulfonylurea use reduces neuroprotection by KATP channels in ischemic events and increases stroke risk in T2D patients as compared to other anti-diabetic drugs.

3-C -118 A novel substrate for preclinical models of cell-based therapy for Parkinson?s disease

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The potential of cell-based therapies for Parkinson's disease (PD) has been recognized for decades, however researchers have yet to define an ideal substrate for transplantation. Our lab has previously shown that brain-derived progenitor cells (BDPCs) can be generated from small brain biopsies from human neurosurgical patients. These cells offer a favourable substrate for transplantation given their neural origin, immunological properties and endogenous expression of neurotrophic factors. The current work sought to determine whether BDPCs could be generated from rodent cortical tissue and if such cells exhibit a similar phenotype to human BDPCs. Small cortical samples from adult Fischer rats were processed and cultured using our previously described protocol for human samples. Using Western Blot and immunocytochemistry we critically evaluated expression of a panel of lineage-specific markers as well as several neurotrophic factors. Neurotrophic factor expression was further evaluated using PCR. Expansion of cells was evident one week after culture of primary rodent brain tissue. Cells were readily passaged and express a broad panel of lineage markers similar to their human analogue. Expression of multiple neurotrophic factors was detected in cells as well as in cell media. In conclusion, BDPCs can be isolated from adult rat cortical tissue and share phenotypic markers and neurotrophic factors with human BDPCs. The present study characterizes a population of cells that can be used to evaluate therapeutic potential of syngeneic BDPCs transplants in preclinical models of PD.

3-C -119 Modulation of mitochondrial function using overexpression of transcription factors as neuroprotective therapy for Parkinson's disease

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Degeneration of midbrain dopamine neurons is the main pathological hallmark of Parkinson's disease (PD). The etiologies of PD remain unsolved, but mitochondrial dysfunction emerges as a central mechanism in inherited, sporadic, and toxin-induced PD. We previously showed that sustained expression of LIM-homeodomain transcription factors Lmx1a and Lmx1b is required for the survival of adult midbrain dopaminergic (mDA) neurons. We found that Lmx1a and Lmx1b control expression of key genes involved in mitochondrial functions and their ablation results in impaired respiratory chain activity, increased oxidative stress and mitochondrial DNA damage. The Nuclear respiratory factor-1 (Nrf1), an essential transcription factor for the integration of nuclear- and mitochondrial-encoded gene transcription, was significantly decrease in Lmx1a/b cKO mice. I this study, we tested the hypothesis that AAV-mediated overexpression of Lmx1a/b or Nrf1 in adult nigral dopaminergic neurons is neuroprotective in mouse models of Parkinson disease. Preliminary behavioral analysis showed that mice in which Lmx1a/b or Nrf1 is overexpressed in mDA neurons perform better than controls after unilateral 6-OHDA lesion. Stereological neuronal counting also indicates that forced expression of Lmx1a/b and Nrf1 is neuroprotective. Ex vivo intrinsic mitochondrial respiratory capacity measurements in permeabilized mDA samples using high-resolution respirometry show that modulation of mitochondrial functions could be targeted to halt the progression of neurodegeneration in model of PD.

3-C -120 PEG-Enzyme for treatment of neurodegenerative diseases

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Glutamate, as the major excitatory neurotransmitter in the brain, is involved in many aspects of brain function. During neurodegenerative diseases, the high levels of glutamate induces excitotoxicity and leads to neuronal death and loss of cognitive function. Some studies have suggested that reducing blood levels of glutamate could induce efflux from the brain to the blood therefore leads to the decrease in its cerebral concentrations. Our hypothesis is that the use of enzyme-polymer bio-conjugates could be interesting for the treatment of neurodegenerative diseases. The glutamate dehydrogenase (GDH) via its catalytic activity, will consume the excess glutamate and the biocompatible polymer selected, which is polyethylene glycol (PEG), will increase the duration of circulatory half-life. We propose, therefore, to synthesize conjugates GDH-PEG, to validate the maintenance of enzymatic activity and check their therapeutic efficacy. For this purpose, we conjugate PEG on the surface of the GDH (by using 2 ratios), we validate the reaction by visualization of our bio conjugates by SDS PAGE and by separating them with Size exclusion chromatography. After that we characterize the number of PEG per GDH by NMR and we evaluate the enzymatic activity before and after bio-conjugation. Our results demonstrate that the use of different Ratio allows us to have variable number of PEG grafted on the surface of our enzyme. After PEGylation, we showed that the enzyme activity is maintained. Currently, we are doing in vivo tests in rat's models to evaluate the effectiveness of our treatment.

3-C -121 Locomotor and synaptic abnormalities in a zebrafish tardbp (tdp-43) knockout model.

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[1]CRCHUM, [2]Montreal Neurological Insitiute, [3]CRCHUM, Universite de Montreal

Amyotrophic lateral sclerosis(ALS) is a debilitating neurodegenerative disease affecting upper and lower motor neurons. Before clinical manifestation of ALS, it is believed that significant changes occur at the

neuromuscular junctions(NMJ). We and other groups believe therapeutic strategies should be tailored to targeting neuronal dysfunction arising at the NMJs in individuals with this disease. Mutations in TARDBP(encoding TDP-43) have been associated with familial and sporadic forms of ALS. To investigate the biological function of TDP-43 we generated a zebrafish tardbp knockout model. Zebrafish possess two orthologs of TARDBP, tardbp(encoding tdp-43) and tardbpl(encoding tdp-43l). In this study a loss of function model was generated by knocking out (KO) both orthologs. Initial examination of two day old double KO embryos revealed reduced motility, lack of pigmentation, defective vasculature and decreased life span. A previous study using a zebrafish model transiently expressing mutant human TDP-43 displayed altered synaptic activity at the NMJs. To gain further insight into the synaptic physiology at the NMJ in our tdp-43 KO model we performed whole-cell voltage clamp recordings on embryonic fast-twitch muscle cells and recorded spontaneous miniature endplate currents(mEPCs). Previous studies hint at the potential of voltage dependent calcium channel (VDCC) agonists and AMPA antagonists in rescuing some of the synaptic abnormalities generated by expression of mutant TDP-43.b However a similar rescue effect at the NMJ in our double KO model remains to be determined.

3-C -122 A neural pathway controlling the motivation to move

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A dominant feature of neuropsychiatic disorders, such as depression and Parkinson?s disease, is reduced motivation to initiate motor function. The neural basis for this phenomenon is not well understood. Here, using optogenetic manipulations in live behaving rats, our objective was to examine the pathway from the lateral habenula, which is excitatory and hyperexcited in depressed states, to the rostromedial tegmental nucleus, which inhibits dopamine centers (LHb-RMTg), in motivated behavioral tasks. In the forced swim test, used to screen drugs for treating human depression, activation (or inhibition) of the LHb-RMTg acutely and reversibly reduces (or increases) mobility, acting particularly by modifying initiation of movement. In appetitive operant tasks, activation of the LHb-RMTg decreases motivation to gain work-demanding sucrose rewards while having no effect on hedonic properties of sucrose. Notably, LHb-RMTg activation has no impact on motor performance and promotes passive avoidance; results precluding the view that LHb-RMTg stimulation merely causes a general motor deficit. These results indicate that the LHb-RMTg pathway encodes signals that, when activated, decreases the motivation to move. Hyperactivation of this pathway may be central in motivational deficits commonly observed in neuropsychiatric diseases.

3-C -123 The Effects of Abeta Oligomers on the Regulation of Protein Synthesis

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Background: Synapse loss is a key pathophysiological feature of Alzheimer's disease (AD) and the best correlate of cognitive decline in AD patients. Nevertheless, the specific mechanisms that mediate reduction of synaptic proteins levels and, ultimately, synapse elimination in AD, remain to be fully understood. Decreased protein synthesis is a well-known feature of AD that could explain the reduction on synaptic protein levels. However, the interplay between the many regulators of protein translation are not yet well established on the course of the disease. There is also a controversy in the literature on the levels of major regulators of protein translation in AD and their role in the disease. A systematical analysis on translational regulators in different time-points is yet lacking. Methods: Here, we have

investigated the levels of major regulators of protein synthesis using RT-PCR and Western Blotting in experimental models of AD such as hippocampal neuronal culture treated with Aβ oligomers (AβOs) and hippocampi extracted from mice that received intracerebroventricular (i.c.v.) injection of AβOs. Results: We found that AβOs, increasingly recognized as proximal synaptotoxins in AD, trigger decrease in the levels of p eIF4E, p 4E-BP1, p S6K, p S6, p ERK, p mTOR and an increase on the levels of ATF4 in the hippocampi of mice 7 days after receiving an i.c.v. injection of AβOs, but not after 24 h. We also report an increase on FMRP expression and levels in neuronal cultures treated for 24h with AβOs and in synaptosomes isolated from the hippocampi of mice 7 days after rece

3-C -124 The effect of aging and generational stress on T2 relaxation values in the hippocampus

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Introduction: Prenatal stress is associated with cognitive impairments, such as learning and memory and associated changes in neuroanatomy. However, little is known about these effects of generational stress on the aging brain. The aim of this study was to investigate age related changes in an animal model of stress and its implications. Methods: Male Long-Evans rats from a generationally stressed or control lineage were used in this study. In vivo MRI T2-relaxometry measurements were collected and analyzed from the hippocampus (HPC) of adult and aged offspring using a 4.7 T MRI. A region of interest (ROI) based analysis was performed from the T2 maps. Quantitative mean grey value (MGV) analysis was also performed. Results: Significant effects of generational stress when compared at different ages were observed. A clear trend of age related changes in T2 values was observed in all lineages. Age related changes in mean grey values were also obtained between young and aged offspring. Discussion: These findings indicate that generational stress may compromise neuronal integrity which could lead to neurodegeneration. All groups investigated exhibited a decrease in T2 value in both ages, with a strong significant change in non-stressed, while milder effects were observed in the stressed offspring.The decrease in mean grey value indicates possible age related neuronal loss. The results of the present study demonstrate that abnormalities in neuronal density of the aging HPC of the rats exposed to generational stress can be detected using T2-relaxometry.

3-C -125 Functional connectivity deficits in Autism Spectrum Disorder following personalized intrinsic network topography mapping

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Recent advances have quantified individually specific variation in brain architecture in healthy individuals using fMRI data. To our knowledge, the effects of individually specific variation in complex brain disorders have not been previously reported. First, we developed a novel approach (Personalized Intrinsic Network topography, PINT) for localizing individually specific resting state networks at large scale. Using the ABIDE dataset's longitudinal subsample (n=34, from two sites), we confirmed that PINT identification intrinsic networks was reproducible in the same individuals over time. Using resting fMRI data from 15 sites of the ABIDE consortium, we found greater variability of spatial locations within resting state networks in the Autism Spectrum Disorder (ASD, n=393) compared to typically developing (n=496). This effect was most prominently noted for regions of the Salience Network. In healthy participants, variability decreased from childhood into adulthood, and increased again in late-life, following a 'U-shaped' pattern, which was not present in those with ASD. Finally, a comparison of intrinsic connectivity between groups revealed that PINT correction decreased the number of hypo-connected regions in ASD, underscoring the importance of accounting for individual variation in the

study of complex brain disorders. Our results provide a new framework for measuring altered brain functioning in neurodevelopmental disorders that may have implications for tracking developmental course, phenotypic heterogeneity, and ultimately treatment response.

3-C -126 The role of sodium channels in multiple sclerosis.

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Axonal degeneration is a non-reversible process in multiple sclerosis (MS), which leads to neurological disabilities including visual impairment. While, the mechanisms underlying this axonal degeneration remain unclear, voltage gated sodium (Nav) channels, have recently been implicated in the etiology of MS. Nav1.6, which is co-localized with Na+/Ca2+ exchanger (NCX) at the nodes of Ranvier in myelinated axons, has been shown to associate with axonal loss following demyelination. It has been suggested that the persistent influx of sodium through Nav1.6 in demyelinated axons may cause the NCX to operate in reverse resulting in increased influx of damaging Ca2+ ions. However, this hypothesis has not been investigated by gene targeting of Nav1.6. Here, we examined if the deletion of Nav1.6 in retinal ganglion cells (RGC) improves axonal survival in mice with experimental autoimmune encephalomyelitis (EAE) an MS-like state. We were able to visualize and quantify Nav1.6-knocked-out RGCs using live imaging and immunohistochemistry prior to and after EAE. We also investigated axonal degeneration by using histology and electron microscopy. Preliminary results suggest that a reduction of Nav1.6 levels is neuroprotective. Furthermore, using Scn8a-dmu+/-mice, which have 50% expression of Nav1.6 compared to WT, we investigated the expression of several genes in the retina that are involved in the pathophysiology of MS, including NCX,Nav1.2, IL-6 and APP (amyloid precursor protein) before and after EAE induction. Our findings thus far are consistent with the proposed hypothesis.

3-C -127 Rapid drug discovery in genetic models of CHARGE Syndrome

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CHARGE Syndrome (CS) is a genetic disorder characterized by a complex array of birth defects, for which there are no cure. We have developed C. elegans and zebrafish models of CS and used them for a phenotypic drug screen of 3850 clinical-approved molecules. The C. elegans model of CS carries a deletion mutation in the gene chd-7 and displays a pronounced impaired movement phenotype, are short-lived and show severe dysmorphia of the GABAergic motor neurons during development, which could explain the motor deficiency. The latter phenotype was exploited in the context of a high-throughput in vivo drug screen of small molecules that suppress mutant CHD7 toxicity and therefore inhibit the onset of this abnormal phenotype in mutant chd-7 C. elegans. Of the more than 3800 drugs that were screened we found 56 compounds capable of rescuing motor deficiency. We classified these positive hits into functional categories, which allowed us to identify possible molecular mechanisms underlying mutations in chd-7. To further gain insights into these mechanisms, we tested specific identified compounds for their ability to improve GABAergic motor neuronal development and extend lifespan of chd-7 mutants. Zebrafish model of CS displays several phenotypes of CS including neural crest-derived phenotypes. We are currently testing lead compounds on the zebrafish vertebrate model of CS. In conclusion, simple animal models are useful for drug discovery for CS and our findings may assist in accelerating the development of drugs for the treatment of CS.

3-C -128 Long-term effects of concussions on psychomotor speed and cognitive control processes during motor sequence learning

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In asymptomatic multiple-concussion athletes, studies evidenced long-term impairments in psychomotor speed, motor sequence learning and cognitive control processes, as indexed by the error-related negativity (ERN). In healthy controls, motor sequence learning during a Serial Reaction Time Task (SRTT) is associated with an increase in ERN amplitude. Objective: To investigate whether concussions effects on cognitive control are associated to sequence learning changes in asymptomatic concussed athletes. Method: 37 athletes (18 control; 19 concussed) completed a SRTT during which continuous EEG activity was recorded. ERN amplitude modulation from early to late learning blocks of the task was measured. Median reaction times were computed to assess psychomotor speed and motor sequence learning. Results: Psychomotor speed was significantly reduced in concussed athletes ($F1, 35 = 4.552$; $p = 0.040$). Accentuated ERN amplitude from early to late learning blocks significantly correlated with overall motor learning in control athletes ($r = 0.58$; $p = 0.012$). In contrast, ERN amplitude was found to decrease significantly with task progression in concussed athletes ($F 1, 35 = 8.355$; $p = 0.007$) who nonetheless achieved normal motor sequence learning ($F1, 35 = 1.725$; $p = 0.198$). Conclusions: Concussions detrimentally affect psychomotor speed. Unlike control athletes, motor sequence learning in concussed athletes was not associated with ERN amplitude modulation, indicating that cognitive control processes do not centrally contribute to learning of a motor sequence after repeated concussions.

3-C -129 Rab7 palmitoylation is required for efficient endosome-to-TGN trafficking

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Alzheimer's (AD) and Parkinson's (PD) disease are the most common neurodegenerative pathologies in Canada. Within the last several years, it has become clear that the expression level of and mutations in proteins critically important in mediating intracellular trafficking pathways are involved in the pathogenesis of both AD, PD and other neurodegenerative diseases. Retromer mediates endosome-to-Trans Golgi Network (TGN) trafficking. Mutations in and the expression level of retromer have been implicated in the pathogenesis of both PD and AD respectively. Retromer recruitment to endosomes is regulated by Rab7, which coordinates the endosome-to-TGN trafficking of cargo-receptor complexes. We found that Rab7 is palmitoylated and that this modification is not required for membrane anchoring. Palmitoylated Rab7 co-localizes efficiently with and has a higher propensity to interact with retromer than non-palmitoylatable Rab7. The rescue of Rab7 knockout cell line with wild-type Rab7 restores efficient endosome-to-TGN trafficking, while rescue with non-palmitoylatable Rab7 does not. Interestingly, Rab7 palmitoylation does not appear to be required for the degradation of EGF or EGF receptor nor its interaction with its effector RILP. Overall, our results indicate that Rab7 palmitoylation is required for the spatiotemporal recruitment of retromer and its role in mediating efficient endosome-to-TGN trafficking, but not in its function mediating degradation suggesting that this post-translational modification targets Rab7 to a specific function and cellular pathway.

3-C -130 Using a Cyclized SNK Conformation-Specific Antibody to Block the Propagation of Amyloid-β Aggregates Formation

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A growing body of evidence points to soluble Amyloid-β oligomers (AβO) as major agents to neuronal loss in Alzheimer's disease. Their ability to seed regional aggregation spreading makes them a target of choice to halt the propagation of neurodegeneration. 5E3 is a mouse monoclonal antibody that binds to a cyclic Ser-Asn-Lys (cSNK) epitope, hypothesized to be specific to AβO. Previous data from our lab shows that 5E3 recognizes AβO in human AD patients and AD mouse models, and does not bind to Aβ in its monomeric or fibrillar forms. In the current study, our aim was to test the ability of the 5E3 antibody to block AβO aggregation. We hypothesized that 5E3 binding to AβO will prevent aggregation by blocking oligomer formation. Thioflavin T (ThioT) fluorescence assay and immunoblotting were used to track Aβ1-42 aggregation in vitro. The resultant Aβ assemblies were characterized by Transmission Electron Microscopy (TEM). Incubation with 5E3 antibody markedly lengthened the ThioT lag phase of Aβ and diminished the endpoint β-sheet signal after 24hrs. At endpoint, these samples were fractionated by centrifugation and resolved on SDS-PAGE for immunoblotting with a pan-Aβ specific antibody. The analysis on these fractions confirmed that 5E3 blocked Aβ assembly into an insoluble state. Incubation with 5E3 resulted in the retention of Aβ in its non-aggregated form compared to samples incubated without antibody, where Aβ alone aggregated into insoluble fibrils, as shown by TEM. Our data demonstrates that the AβO-specific 5E3 antibody blocks the aggregation of Aβ in vitro.

3-C -131 Effects of Exercise and Light Treatment on Neurogenesis and Spatial Learning in Aged Rats

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Studies have shown that age-related decline in neurogenesis may underlie associated declines in learning and memory and may contribute to some forms of dementia. The objective of this study was to measure spatial memory and neurogenesis in aging rats along with the effectiveness of three treatment conditions that may improve neurogenesis and memory in aging rats. Female and male Long-Evans rats (1 year of age) were split into four groups; control (C), light treatment (L), running-wheel (W), and running-wheel combined with light (W+L). Light treatment consisted of 30 minutes of bright light administered at the beginning of their light cycle. Running wheel treatment consisted of voluntary access to a running wheel. Male rats were tested in the Morris Water Task (MWT) before and after receiving their six-week treatment period. Rats received a Bromodeoxyuridine (BrdU) injection on the fifth week of treatment. BrdU, Doublecortin, and Ki-67 were used to mark newly formed cells in the dentate gyrus. Results indicate that the L, W, and W+L treatment groups all initially had better recall in the MWT compared to the control group. Results from the cell counts suggest that a combination of both W+L yields an elevated rate of neurogenesis. Our results are in accordance with other studies regarding the benefits that light treatment and exercise have on enhancing hippocampal neurogenesis. In summary, our findings show a trend of enhanced spatial learning and neurogenesis in aged rats when treated with physical exercise and light treatment.

3-C -132 Sex-specific effects of creatine supplementation on spatial learning and memory in the 3xTg mouse model of Alzheimer's disease

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Despite its use in clinical trials in other neurodegenerative disorders, creatine has not been tested as a therapy in Alzheimer's disease (AD), characterized by learning and memory deficits. Creatine dysfunction is reported in AD in the hippocampus, a key memory structure. We have shown enhancements in hippocampal-dependent spatial learning and memory in mice with creatine supplementation (CS). To evaluate the effects of CS on hippocampal function and neuropathology in the AD-like brain, 7-month-old male and female triple transgenic (3xTg) mice, an AD model, were assigned a CS (3%, w/w) or control diet (8 wks), followed by training in the hippocampal-dependent Morris water maze (MWM). Hyperphosphorylated tau levels were assessed with immunoblotting to indicate hippocampal neurofibrillary tangle (NFT) extent. Amyloid beta (Aß) plaques were detected with Congo red staining. Factorial ANOVAs (sex as a factor) revealed a significant decrease in escape latency in females ($p < 0.05$), in contrast to increased latency in males ($p < 0.05$) with CS during MWM acquisition. Entries into the target quadrant on the memory retention trial were similar in female mice regardless of diet ($p > 0.05$) but decreased with CS in males ($p < 0.01$). Tau levels were reduced in CS females ($p < 0.05$). Congo red experiments to detect Aß plaques are ongoing. Data indicate sex-specific effects of CS in 3xTg mice, with enhanced cognition in females and impairments in males. Our results suggest that CS may offer cognitive benefits and protection from neuropathology in women with early-stage AD.

3-C -133 Examining the Effects of Lithium and Valproate on Max-gene expression: Implications in Bipolar Disorder (A Study-in-Progress)

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Bipolar disorder (BD) is a debilitating mental illness affecting approximately 2% of the world's population. Current options in treating the disease revolve around two main drugs - lithium and valproic acid (VPA). Recently shown to be elevated in untreated bipolar patients is Max, a gene whose protein associates with other proteins and transcription factors, notably Myc. The Max-Myc heterodimer activates transcription, and Myc disregulation specifically is associated with tumour initiation and progression. There is evidence to suggest that this disease consists of significant changes in cellular transduction mechanisms. Patients with BD have an elevated risk of comorbid, chronic illnesses, including anxiety and substance use disorders. Our study administered lithium chloride (LiCl) (n=8), VPA (n=8) and a control vehicle (n=6) to male Sprague-Dawley rats to determine the effects of these drugs on the expression of Max and its associated proteins in key brain regions. The drugs doses were administered twice a day for 14 days. Through quantitative PCRs, preliminary results showed a significant decrease in Max gene-expression in the rat cortex with VPA administration, and a substantial decrease with LiCl administration. Further studies are warranted to investigate the role of Max and Myc genes in relation to the mechanism of action of mood stabilizers. This work has the potential to elucidate the mechanisms of bipolar disorder, advancing research into better, more specific treatments for the disease. This work is funded by OMHF.

3-C -134 Impaired frontal beta desynchronization during an incentive motivation task in apathetic patients with Parkinson's disease

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Apathy, independent of depression, is a common non-motor symptom of Parkinson's disease (PD) that is poorly understood, difficult to quantify, and resistant to therapy. We explored whether beta frequency oscillations, which normally desynchronize during incentivized motor tasks but are characteristically excessive in PD, would be altered in apathetic compared to non-apathetic PD subjects. Both PD subjects

with apathy (n=3) and no apathy (n=3) performed a squeeze grip task to varying monetary incentives ($1, $10, $50) while EEG data were recorded. First, the maximum money earnable in each trial was visually presented. Then, the subject was required to squeeze a hand grip. The amount of money earned on each trial was dependent upon the grip force response (GFR), calibrated to each subject's maximum squeeze force. 15 trials of each monetary value were performed (45 total). Results showed that mean GFR of apathetic subjects was consistently lower than non-apathetic subjects for all monetary values presented. We performed time-frequency analysis on epochs time-locked to the visual presentation of money. Apathetic PD subjects showed reduced frontal beta desynchronization compared to non-apathetic PD subjects. While preliminary, our results suggest that apathy in PD is associated with a reduction in incentivized motor responses and impaired beta desynchronization in frontal brain regions, likely involving the anterior cingulate cortex, which is dysfunctional in apathy. Frontal beta desynchronization may additionally serve as a potential biomarker for apathy in PD.

3-C -135 Targeted delivery of a tropomyosin receptor kinase A ligand to the brain using focused ultrasound

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Among the neuronal populations that degenerate in Alzheimer?s disease (AD), cholinergic loss most closely correlates with declines in synaptic number and cognitive function. Nerve growth factor (NGF) has been shown to promote neuronal survival and synaptic plasticity, and thereby represents a promising therapy for AD. However, therapeutic efficacy of NGF is limited by its inability to cross the blood-brain barrier (BBB), its short half-life, and adverse effects triggered by NGF activation of p75 receptor in the absence of tropomyosin receptor kinase A (TrkA). In comparison to NGF, ligands designed to maximize TrkA activation may be preferable. D3 is a small, stable, high-affinity agonist of TrkA. However, like NGF, it does not cross the BBB. Here, we use MRI-guided focused ultrasound (MRIgFUS) for non-invasive, transient and localized BBB opening, to facilitate delivery of D3 in targeted regions. We aim to promote TrkA activation and cholinergic function by targeted delivery of D3 using MRIgFUS. We used a transgenic (Tg) mouse model of AD with deficits related to cholinergic transmission. Briefly, Tg mice and non-Tg littermates were injected intravenously with D3 and MRIgFUS applied to brain regions where TrkA is expressed. Expression of TrkA signaling and key downstream effectors were quantified for mRNA, protein and phosphorylation. We observed an increase in TrkA phosphorylation and downstream signaling activation after treatment. These results demonstrate the therapeutic efficacy of the TrkA-specific agonist, D3, combined with MRIgFUS delivery in a mouse model of AD.

3-C -136 Synaptic Ras-GTPase Activating Protein Facilitates Dopamine D1 Receptor-mediated GABAergic Interneuron Migration and Associative Learning

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Dopamine D1 receptors (D1Rs) have been shown to play a role in GABAergic interneuron migration. However, neither the molecular mechanism underlying this process nor the pathophysiological consequence due to a disruption in this process during development remains unclear. Here we report a novel interaction between D1Rs and Synaptic Ras-GTPase Activating Protein (SynGAP), which facilitates D1R membrane expression and D1R-mediated downstream signaling pathways including phosphorylation of protein kinase A and P38 mitogen-activated protein kinase. These effects were blocked in the presence of an interfering peptide (TAT-D1Rpep) that specifically disrupts the D1R-

SynGAP interaction. Interestingly, disrupting this complex during embryonic development resulted in pronounced interneuron tangential migration deficits, possibly due to altered actin and microtubule dynamics. More importantly, administration of TAT-D1Rpep to pregnant mice led to abnormalities in associative learning, pre-pulse inhibition, and sociability in the offspring mice. Our findings here can better understand and add values to the therapeutic development for GABAergic interneuron migration-related diseases, such as schizophrenia and ASD.

D – Sensory and Motor Systems

3-D -137 Palinopallesthesia: A New Syndrome

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Introduction: Persistent perception of pallesthesia after discontinuation of vibratory stimulus, palinopallesthesia, has not heretofore been described. Methods:Case Study: A 54 year old right handed female with a lifelong history of distorted taste presented with a 6 year history of diabetes mellitus type 2. Since then her taste and smell seems better than normal and at times she can smell the difference in colors. After consuming food or smelling odors there will be a persistent taste or smell, respectively. Light exposure induces an enduring photopic afterimage. Since 20 years old, after mowing the lawn or using the snow blower, her hands will vibrate for an additional half hour, which is reduced with movement. Results: With brief application of the Rydel-Seiffer Tuning Fork to the lateral malleolus, vibration was normal. However, on removal, the vibration persisted for 2-3 minutes. Repetitive testing elicited similar persistent sensation. Abnormalities in Neurologic Examination: Tandem gait unstable. Decreased proprioception, temperature, and pin prick in both lower extremities, up to the thighs. Reflexes: 0-1 throughout. Other: MRI with and without infusion: normal. Discussion - Pallesthesia is the sensory perspicacity of vibration (Barker, 1920). In the Vibration Hand Syndrome, after prolong exposure to industrial vibratory stimuli, sensory loss is discerned, but vibratory sensation does not persist after exposure. Presence of palinopallesthesia warrants further neurologic evaluation for evidence of subtle peripheral nerve dysfunction.

3-D -138 Reduced acoustic startle response and peripheral hearing loss in the 5xFAD mouse model of Alzheimer?s disease.

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Hearing dysfunction has been associated with Alzheimer's disease in humans, but there is little data on the auditory function of mouse models of Alzheimer's disease. Furthermore, characterization of hearing ability in mouse models is needed to ensure that tests of cognition that use auditory stimuli are not confounded by hearing dysfunction. Therefore we assessed acoustic startle response and pre-pulse inhibition in the double transgenic 5xFAD mouse model of Alzheimer's disease from 3-4 to 16 months of age. The 5xFAD mice demonstrated an age-related decline in acoustic startle as early as 3-4 months of age. We subsequently tested Auditory Brainstem Response (ABR) thresholds at 4 and 13-14 months of age using tone-bursts at frequencies of 2- 32 kHz. The 5xFAD mice showed increased ABR thresholds for tone-bursts between 8 and 32Khz at 13-14 months of age. Finally, cochleae were extracted and basilar membranes were dissected to count hair cell loss across the cochlea. The 5xFAD mice showed significantly greater loss of both inner and outer hair cells at the apical and basal ends of the basilar

membrane than wildtype mice at 15-16 months of age. These results indicate that the 5xFAD mouse model of Alzheimer's disease shows age-related decreases in acoustic startle responses, which are at least partially due to age-related peripheral hearing loss. Therefore, we caution against the use of cognitive tests that rely on audition in 5xFAD mice over 3- 4 months of age, without first confirming that performance is not confounded by hearing dysfunction.

3-D -139 Serotonin mediates efficient adaptive optimized coding of second-order natural stimuli

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Growing evidence suggests that neural systems are adapted to their environment in order to optimally encode natural sensory stimuli with a given set of statistics. The mechanisms underlying this adaptation are, however, poorly understood in general. Previous studies in an array of sensory systems have shown that neural responses are optimally tuned utilizing various strategies in order to efficiently process sensory information to enable matched behavioural perception to the stimulus statistics. However, what happens when those statistics change over time? Here we show, using the weakly-electric fish Apteronotus leptorhynchus that the electrosensory system can adapt to a given environment with differential stimulus statistics. Using a combination of electrophysiology, behavioural paradigms, and pharmacology, we demonstrate that adaptation takes place at the single-neuron level, leading to an adaptation at the behavioural level matching the stimulus statistics. Furthermore, we demonstrate that this adaptation requires feedback processes from the telencephalon, mediated by the release of serotonin (5-HT) onto 5-HT2 receptors located on the pyramidal cells of the electrosensory lateral line lobe (ELL). Therefore, our study reveals the circuitry leading to adaptation to natural sensory stimuli, as well as a novel function of 5-HT2 receptors in regulating adaptive optimized coding. Due to the ubiquity and similarities in homology of 5-HT2 receptors in weakly-electric fish and mammals, it is likely that our results are generally applicable across sensory systems and species.

3-D -140 Olfactory learning-induced plasticity-related protein activity varies across brain regions

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Previous research has contributed to our understanding of the role of many molecular mechanisms involved in long-term memory (LTM). This research has also suggested that LTM depends as much on the temporal specificity of these mechanisms as on their downstream effects. It is yet unclear how the timing of these mechanisms, as well as their coordinated activity across the multiple brain regions, are involved in learning. In the present study, we took a step toward characterizing the timecourse of several molecular mechanisms across multiple brain regions. We trained mice on an associative odour learning task for 1, 2, 4, or 6 days. We collected the olfactory bulb, striatum, hippocampus, cortex, and cerebellum from the mice on each day prior to training, immediately after training, or 15, 30, or 60 minutes after training. We developed a robotic protocol for high-throughput sample processing that allowed us to analyze by quantitative RT-PCR the mRNA levels in over 300 individual specimens for several plasticity-related proteins (PRPs), including: bdnf; the intracellular signaling cascades, erk1 and erk2; the transcription factor, creb1; and the immediate early genes, arc, fos, and erg1. We found that learning-responsive transcription differed between genes, and that PRP timecourses differed as a function of brain region. Building upon these findings, we are now adapting our approach to enable a

global analysis of changes in gene expression in these samples, with the goal of elucidating the composite molecular changes that accompany LTM.

3-D -141 Dorsolateral prefrontal cortex activities following deactivation of anterior cingulate cortex in an antisaccade task in monkeys

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Well regulated saccadic eye movements are essential to daily life. While simple, visually-guided saccades do not activate the dorsolateral prefrontal cortex (dlPFC) and the anterior cingulate cortex (ACC) in functional imaging studies, both areas are engaged when task demands increase (Brown et al., 2004, DeSouza et al., 2003, McDowell et al.,2008, Sweeney et al., 1996). For instance, both regions are active during the preparatory but not the response period in the antisaccade task (DeSouza et al., 2003, Ford et al., 2005, Brown et al., 2007). Here we trained macaque monkeys to perform alternating blocks of prosaccade and antisaccade trials. Without explicit instruction, the animals were able to shift their response strategy within 3-4 trials based on reward feedback. We recorded local field potentials (LFPs) and single neuron activity from electrode arrays in the dlPFC during the task, both before and after bilateral deactivation of the ACC via implanted cooling loops. Both animals generated significantly more direction errors on the antisaccade trials, while performing at the same level on prosaccade trials. Interestingly, the saccadic reaction time in both types of trials increased as a result of ACC cooling. The most striking effect was found in the dlPFC, where LFP powers were drastically weakened across all frequencies. Individual dlPFC neurons also exhibited a dramatic reduction in spiking activities. Our findings showcase the importance of ACC inputs in driving dlPFC activities, and the critical roles played by both regions in antisaccades.

3-D -142 Modeling pain caused by rattlesnake venom and beyond

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Animal venoms are rich reservoirs of predatory and defensive ingredients. The ingredients from different species amounts to millions of peptides/proteins and small molecules; some of which are species-specific and others are evolutionary-conserved. Many of these ingredients have proven to have useful pharmacological applications in basic science research, and in the near future, they are likely to facilitate disease-management in the clinic. Pain induction is an evolutionary-conserved strategy by which most venomous animals defend themselves against predators. However, species-specific peptides have been identified to be responsible for pain caused by honey bee and Texas coral snake venoms. Here, we report that small molecules rather than peptides are responsible for pain caused by rattlesnake venom. Mice lightly-anesthetized with isoflurane were subjected to intra-plantar injection of control buffer or venom into their hind-paws. Under this light-anesthesia, needle-poking and injection of the control buffer produced no response; however, the mice still exerted withdrawal-reflex to a brief toe-pinch. Injection of rattlesnake venom caused a pronounced withdrawal response and progressive swelling of the injected-paw. Removal of peptides/proteins from the crude venom completely prevented paw-swelling, but failed to prevent the pain response. Finally, these molecules are conserved amongst animal species, and also found in synovial fluids extracted from chronic pain patients in our hospital. The reported findings thus have implications beyond pain caused by rattlesnake bites.

3-D -143 Development of presynaptic inhibition to dI3 INs involved in the maturation of hand grasp

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Maturation of motor control, including movements that can be autonomously generated by spinal circuits, relies on the development of key inputs to spinal circuitry. In particular, the development of supraspinal, sensory and motor fibers integrate to form organized spinal circuits capable of producing skilled movements. Primitive reflexes such as the palmar grasp reflex (PGR) are known to disappear during development; presumably giving way to more volitional control of hand grasping. However, the underlying changes to the spinal circuitry responsible for this transition remain to be determined. dI3 INs, a class of dorsal spinal interneurons, have positioned themselves as key mediators of reflexive grasping in early development and grasping in adult mice. The first aim of the study focused on determining the developmental time point at which the PGR disappeared. We demonstrated that the PGR was lost by the third week of development. The second aim of this study focused on identifying changes in sensory innervation, presynaptic inhibition and supraspinal excitation to dI3 INs that might account for the loss of this reflex. We demonstrated that while sensory innervation remained constant during development, presynaptic inhibitory terminals onto sensory afferents were found. In addition, we report that dI3 INs receive decreasing corticospinal (CST) input during development. While these developmental changes do not fully account for the disappearance of the PGR, they provide valuable insights into how a reflex centered on a particular population develops.

3-D -144 Efficacy of Motor Imagery in Motor Rehabilitation of Upper Extremity in Multiple Sclerosis

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Aim: Imagination of a physical activity without any associated overt movement, known as motor imagery (MI), has recently proved positive therapeutic effects in Parkinson's and post-stroke patients. This study was designed to evaluate the efficacy of MI in rehabilitating motor tasks in patients suffering from MS. Methods: 24 patients with relapsing-remitting MS were subjected to an immediate pre-treatment and posttreatment single-group study. The ability to perform motor tasks was measured by Nine Hole Peg Test (9HPT), Box and Block Task (BBT), Hand Mental Rotation (HMR), and Mental Chronometry (MC). 10 MI training sessions (60 minutes each) were scheduled for each patient in two weeks. MI training was adjusted according to patient feedback. Results: Six patients were not able to perform MI or continue the experiment, and were excluded from the study. The time required to complete the 9HPT was significantly decreased from 25.15±3.55 seconds before MI training to 22.87±2.65 seconds after MI training ($p=0.003$). The analysis of BBT results revealed that the number of transferred blocks within a certain time was significantly higher after MI training (51.88±6.50) than before (48.13±9.86) ($p=0.02$). The response accuracy rate of HMR was increased from 69.67±15.90 to 84.02±10.31 percent after MI training ($p<0.001$). The difference between imagery and practical MC was significantly decreased from 7.25±2.57 seconds to 3.35±2.43 seconds after MI training ($p<0.001$). Conclusion: MI training led to shorter reaction time, higher performance rate, and more accuracy in motor tasks.

3-D -145 Illuminating the function of inhibitory microcircuits in the zebrafish homolog of olfactory cortex

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The brain creates dynamic representations of the sensory environment by extracting stimulus features at early processing stages and synthesizing more abstract object representations in higher brain areas. We dissect the function of neuronal microcircuits in a higher olfactory brain area to identify elementary computations of basic cortical circuits and to analyze the underlying cellular mechanisms. We use a combination of genetic, electrophysiological and optical approaches to visualize and manipulate different types of interneurons (INs) in the posterior zone of the dorsal telencephalon (Dp) of adult zebrafish. This brain area is homologous to olfactory cortex in mammals and assumed to be involved in olfactory object representations and associative memory. We identified two types of inhibitory INs that have similar electrophysiological properties but are differently connected to other neurons in Dp. Both IN types provide divisive inhibition, a particularly important form of inhibition in auto-associative memory networks, which has so far not been observed in olfactory cortex. In addition, we observe that Dp interneurons are involved in other functions, including separation of similar odor representations, representation of odor objects, and in regulation of neuronal plasticity.

3-D -146 Targeted high-throughput screening of olivocerebellar motor circuitry genes in essential tremor

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Background: Essential Tremor (ET) is a prevalent neurological disorder of unknown etiology that is characterized by the presence of action tremors occurring during voluntary motion and affecting primarily the upper limbs. Twin studies revealed variable concordance in ET but are nonetheless suggesting that genetic risk factors likely contribute to the pathology. To date, no gene was reproducibly reported to cause ET across unrelated cohorts which is likely due to the genetic heterogeneity of the disorder. However, mounting evidence currently suggests dysfunctions affecting the olivocerebellar motor circuitry as the primary source of tremors. Hypothesis: Genes that are phylogenetically conserved for their expressions in the olivocerebellar circuitry are susceptible to present genetic variations that would be ET risk factors. Methods: A preliminary list of 11 candidate genes that were selected based on their high level of expression in the olivocerebellar circuitry in both human and mouse has been generated using publicly available data from the Allen Brain Atlas. The 11 genes from this list, which noticeably appear to encode several proteins involved in calcium and glutamate signaling pathways, have been screened for the presence of genetic variations in a cohort of cases and controls. The mutation screen has been done using a Molecular Inversion Probes (MIPs) capture methodology. Outcome: this approach has not only the potential in identifying novel ET risk factors but could also link this pathology to a particular signaling pathway.

3-D -147 The smell of fear: Pheromonal transmission of fear in adult rats

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Pheromone release from a stressed animal can affect conspecific behaviour. Adult male and female Sprague Dawley rats were assigned into four groups. "O-/S+" and "O+/S- alone" were singly housed control groups exposed either to shock or terpinene odor (T) respectively. "O+/S+" rats were conditioned to associate T with a footshock and pair-housed with "O+/S- together" rats exposed only to T. Both O+/S+ and O+/S- together showed significantly increased freezing behaviour to T but not to a control odor octanol (Oc). This suggests the conditioned rats communicated a specific fear to their

companion. To determine if these two differentially acquired memories utilize distinct neural circuitries Homer/Arc compartmental cellular analysis of temporal activity by in situ hybridization (catFISH) was used to map cells active to T and Oc across several regions of the brain. O+/S- together rats show a significantly higher proportion of cells responding to T in the accessory olfactory bulb (AOB). Comparatively O+/S+ rats show a similar trend in the main olfactory bulb (MOB). AOB pathway activation is consistent with pheromone transmission. Both O+/S+ and O+/S- together rats show a significant decrease in the proportion of cells responding to T in the basolateral amygdala (BLA), an area where others have found decreased neural excitability following aversive conditioning. Rats may be able to communicate conditioned fear memories through pheromones resulting in a distinct type of learning involving the AOB, while BLA involvement may be common to both types of fear memory.

3-D -148 Effectiveness of Tetrodotoxin in Promoting Anatomical Recovery from Monocular Deprivation in Kittens

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Monocular deprivation (MD) by closure of the lids of one eyelid during the critical period of visual development precipitates neuronal alterations in the lateral geniculate nucleus (LGN) of kittens that include a significant decrease in axon terminals and dendritic fields that are reflected by reduced neuron soma size within deprived layers. In this study, we examined the effectiveness of binocular retinal inactivation to promote balanced anatomical recovery within the eye-specific layers of the kitten LGN. After 7 days of MD animals were intravitreally injected with tetrodotoxin (TTX) to abolish retinal activity in both eyes. Neuron soma sizes were measured stereologically from sections of LGN across increasing durations of binocular inactivation that extended to 10 days. The 16% reduction in deprived neuron size produced by 7 days of MD was erased following 10 days of binocular inactivation. Although the overall size of neurons was slightly reduced following retinal inactivation, balanced neuron size between eye-specific layers was restored to normal. Following 10 days of binocular inactivation, neurons were considerably larger than those from animals subjected to the same period of monocular inactivation, indicating a true recovery. These results suggest that binocular retinal inactivation recapitulates the plasticity-enhancing effects of another binocular treatment, dark exposure, by way of restoration of balanced competition between eye-specific inputs that fosters cooperative anatomical development and sets the stage for functional recovery.

3-D -149 Functional contribution of the mesencephalic locomotor region to locomotor control

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The Mesencephalic Locomotor Region (MLR) is a key supraspinal locomotor center to initiate and improve locomotor functions. Its anatomical correlate has been initially identified as the cuneiform nucleus (CnF), a cluster of glutamatergic (VGluT2) neurons, and the pedonculopontine nucleus (PPN), a cluster of glutamatergic and cholinergic (ChAT) neurons. However, there is still an on-going debate about the exact location of this supraspinal locomotor center. Combining kinematic and electromyographic recordings with optogenetic manipulations (ChR2 and NpHR3) in transgenic mice, we investigate the functional contribution of VGluT2 or ChAT neurons of the CnF or PPN to locomotion. Short photostimulations of VGluT2 neurons of the CnF or PPN evoked short-latency excitatory motor responses in flexors and extensors during the swing phase, and inhibitory ones in extensors during the stance phase. In contrast, short photostimulations of ChAT PPN neurons prolonged the duration of the extensor burst. Long photostimulations of VGluT2 CnF neurons reset the locomotor rhythm and give rise

to gallop and full-bound, while activation of VGluT2 or ChAT PPN neurons slowed down the rhythm and induced slow-walking gaits. Interestingly, long photoinhibitions of the VGluT2 CnF or VGluT2/ChAT PPN decreased the locomotor rhythm. By their distinct effects on the locomotor pattern and rhythm, glutamatergic CnF neurons contribute to running gaits, while glutamatergic and to some extent cholinergic PPN neurons induce walking gaits.

3-D -150 Decoding of spatio-temporal olfactory codes: when neural coding predicts decoder?s connectome.

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In the antennal lobe of moths, the identity of odor signals is encoded via a spatio-temporal code: which neurons are active at what time becomes a sort of "QR code" of the odor's identity. The activity of the antennal lobe's Projection Neurons will vary as a function of odor identity, but also intensity. The target of these projection neurons, the Kenyon cells of the mushroom bodies, are fairly selective for specific odors, acting as odor detectors. We used this system to test a new decoding analysis. While many sophisticated neural coding-decoding methods are available, our goal was to improve the tools widely used by experimental sensory neuroscientists. Our initial analysis was based on 3 main-stream decoding techniques: an unsupervised learning network (Self-Organizing Map), the Euclidian distance between neural representations, and the Spike Distance Metric described by van Rossum et al. Combining the advantages of each, while retaining the facility and the familiarity that researcher might have with these techniques, we developed a new method that quantifies how accurately a signal's identity can be decoded. Notably our techniques allow to determine the efficient connection patterns between the coding population and the decoder. For the moth olfactory system, our analysis demonstrates that having a decoder strongly connected to roughly 10 projection neurons would lead to accurate odor identification, which matches the known anatomy of the system. Our method can be used to analyze any sensory coding-decoding network and can incorporate plasticity effects.

3-D -151 Single-axon tracing study of the hyperdirect pathway in monkeys

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This single-axon tracing study provides the first detailed description of axons that form the so-called hyperdirect pathway in monkeys. These axons, which arise from motor cortex and project to the subthalamic nucleus (STN), were studied individually in cynomolgus monkeys (Macaca fascicularis) following microiontophoretic injections of biotinylated dextran amine in cortical layer V of the M1 forelimb area. Singly-labeled axons were reconstructed in three dimensions from serial sections using a computerized image analysis system. The M1 innervation of the STN derives essentially from collaterals of long-ranged corticofugal axons en route to the brainstem. After leaving M1, these large caliber (1.7-3.7 µm) axons enter the internal capsule and travel between the caudate nucleus and putamen without leaving collaterals to the striatum. More ventrally, they emit a thin collateral that runs lateromedially within the dorsal region of the STN, providing "boutons en passant" within the sensorimotor territory of the nucleus. In some cases, the lateromedially coursing collateral emits several thinner and varicose branches that plunge ventrally into the STN. In other cases, its medial tip invades dorsally the lenticular fasciculus and emits few beaded axonal branches in the zona incerta, whereas in still other cases the collateral runs as far caudally as the retrorubral field. This study provides the first detailed depiction of the hyperdirect pathway in primates, a cortico-basal ganglia projection that appears to contribute to the therapeutic effect of STN deep brain stimulation.

3-D -152 The reciprocal relationship between somatosensory and object processing

Chelsea Ekstrand[1], Josh Neudorf[1], Ron Borowsky[1]
[1]University of Saskatchewan

Prevalent theories of semantic processing assert that the sensorimotor system plays a functional role in the semantic processing of manipulable objects. While motor execution has been shown to impact object processing, involvement of the somatosensory system has remained relatively unexplored. Therefore, we developed two novel priming paradigms. In Experiment 1, participants received a vibratory hand prime (on half the trials) prior to viewing a picture of either an object interacted primarily with the hand (e.g., a cup) or the foot (e.g., a soccer ball) and reported how they would interact with it. In Experiment 2, the same objects became the prime and participants were required to identify whether the vibratory stimulation occurred to their hand or foot. In both experiments, somatosensory priming effects arose for the hand objects, while foot objects showed no priming benefits. These results suggest that object semantic knowledge is bidirectionally interactive with the somatosensory system. Implications for differential results between hand and foot objects will also be discussed.

3-D -153 Voluntary running exercise attenuates behavioural signs of pain and reduces pathological nerve sprouting in intervertebral discs in a mouse model of low back pain

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[1]McGill University

Aim: Persistent low back pain (LBP) causes more global disability than any other condition. Due to the limitations of medications, patients seek alternative treatments such as exercise, yoga and meditation. SPARC (Secreted Protein, Acidic, Rich in Cysteine), an extracellular matrix protein, plays important roles in intervertebral disc (IVD) integrity. SPARC-null mice display accelerated disc degeneration associated with behavioral signs of axial and radiating LBP and local nerve sprouting. In this study, we investigated how increased physical activity relieves LBP symptoms in the SPARC-null mouse model. Methods: 8-month old SPARC-null and age-matched wild-type control mice had free access to a running or secured (sedentary) wheel for 4 months. Behavioral assays were performed to assess axial (grip test) and radiating (von Frey & acetone tests) discomfort. Lumbar IVD height and shape were analyzed by X-ray images. Innervation in lumbar discs was measured by PGP9.5- and CGRP-immunohistochemistry (-ir). Results: Axial and radiating pain in SPARC-null mice were reduced by running. X-rays confirmed altered disc shape and reduced disc height in SPARC-null mice; running reversed the former. The increased nerve fiber density observed in degenerating SPARC-null discs returned towards normal values following running. Conclusion: This study addresses the beneficial effects of running for LBP and its underlying mechanisms. In a pre-clinical model of LBP, both increased disc innervation and behavioural signs of pain were reversed by voluntary running exercise.

3-D -154 Associative Cortico-Muscular Stimulation to Induce Persistent Corticospinal Plasticity in Rodents

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Paired associative stimulation (PAS) is an experimental paradigm in which neuronal stimulation is used to activate two areas of the nervous system synchronously, with the goal of promoting long term plasticity. According to the classic rules of spike-timing dependent plasticity, the efficacy of PAS is linked to the precise and systematic timing of pre- and post-synaptic potentials. Rate-based plasticity models,

however, suggest that postsynaptic firing rate is the determinant factor in predicting the direction (long term potentiation vs depression) and amplitude of the plastic effects. In humans, there are early indications that corticospinal potentiation induced by pairing transcranial magnetic and peripheral nerve stimulation may have a clinically relevant therapeutic effect. Despite the large body of work on synaptic plasticity at the cellular and molecular levels, the principles by which neuronal plasticity can be guided using stimulation in awake and behaving subjects are still poorly understood. Here, we systematically examined the effectiveness of a wide range of PAS parameters (stimulation frequency, amplitude, interstimulus interval, number of repetitions) to induce persistent changes in corticospinal excitability in a rodent model. Our study will provide a better understanding of the rules governing neuronal plasticity at the system level. Ultimately, we aim at identifying the most promising approaches for the implementation of a therapeutic strategy applicable to people with neurological disorders affecting the motor system.

3-D -155 Visual saliency response in the superficial and intermediate superior colliculus.

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[1]Queen's University, [2]University of Southern California

Cognitive and computational neuroscience postulates the existence of a visual saliency map and a priority map (combination of bottom-up saliency and top-down relevance) to guide orienting behavior. We hypothesize that the midbrain superior colliculus (SC) embodies the role of both a saliency map and a priority map compartmentalized in the superficial (SCs) and intermediate (SCi) layers, respectively. We compared monkey SCs and SCi firing rate and local field potential (LFP) in response to task-irrelevant but visually salient stimuli presented as a wide-field "pop-out" array. We randomly interleaved 0 to 4 pop-out items to examine how competition between items would affect saliency representation. We predicted that increasing the number of salient pop-out items from 1 to 4 would result in a systematic decrease in the saliency-evoked response at each pop-out location, because of increased competition. We found that 96% (23/24) of SCs neurons firing rate showed a reliable preference for the visually salient stimuli, but responded similarly in the presence of 1 to 4 pop-out items. A smaller percentage (75%; 24/32) of SCi neurons showed a preference for the salient but irrelevant stimuli, but their response was modulated by the number of pop-out items presented, possibly due to reflexive attentional mechanism. LFP responses of both layers displayed a biphasic response to presentation of an array stimulus that evolved to represent the pop-out item. This separation appeared earlier in the SCs than in the SCi.

3-D -156 Thermal stimulations of the face induce forelimb muscle responses in in vitro preparations of newborn opossums, Monodelphis domestica

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[1]Université de Montréal

Marsupials are born very immature and must attach to the mother's nipples in order to continue their development. The newborn opossum crawls on the mother's belly, unaided by her, using alternate rhythmic movements of the forelimbs (FL). While generated by the spinal cord, these movements must be triggered and sustained by cephalic sensory systems. We previously used in vitro preparation of newborn opossums to show that mechanical pressures applied to the skin induce FL movements. In the present study we tested if temperature, another sensory modality, influences FL movements in in vitro preparations. Puffs of physiological solution at cold (4°C), neutral (23°C) or hot (45°C) temperatures were ejected on the face, and FL responses were observed visually and recorded electromyographically. Ejections of the cold solution always elicited strong bilateral muscle responses, whereas ejections of

neutral and hot solutions elicited responses of lesser amplitude and duration or no response at all. These results show that the newborn opossum is very sensitive to cold temperature and that this sensation can influence FL movements. We then used immunohistochemistry to investigate if TRPM8, a non-selective cation channel known to respond to cold temperatures in Vertebrates, is involved in the cold perception. We found that TRPM8 is not expressed in nervous tissues of newborn opossums. As TRPM8 cannot account for the early motor responses triggered by a cold stimulus in the newborn opossum, further experiments will be performed to reveal these mechanisms.

3-D -157 The Prototypical Spatial Pattern of the Brain during Movie Viewing

Angela Zhang[1], Sebastien Proulx[1], Yiran Chen[1], Hassan Akhavein[1], Reza Farivar[1]
[1]McGill University

Whether our brains operate in the same manner remains a persistent question in neuroscience. Previous studies have shown that subjects viewing the same movie exhibit widespread spatiotemporal correlation during functional magnetic resonance imaging (fMRI). However, previous studies have not considered that the visual system fires in spatial patterns, a feature integral to its complexity. In the current study, we investigated spatial pattern similarity between subjects during movie viewing. We will produce a prototypical map of the visual system, demonstrating which areas of the brain process visual stimuli the same way in different people. Unlike previous studies, we used 3-D movies to maximize realism and clips that minimize narrative to focus on visual processing. Fifty-six subjects watched two 5-minute movie clips from a 3-D movie during an fMRI scan. We calculated the between-subject spatial pattern correlation centered on every voxel of the posterior brain during the clips. High correlation at a voxel means that the space surrounding that voxel has a spatial pattern that looks extremely similar across subjects. A single threshold permutations test was used to test for significance. We found significant spatial correlations between subjects in the majority of early visual cortex, as well as higher visual areas. Our results show that early visual cortex processes information the same way in different people, thereby answering one aspect of the question of whether different brains operate in the same manner.

3-D -158 Distinction of itch and pain sensation by a single population of C-fibers

Behrang Sharif[1], Ariel Ase[2], Alfredo Ribeiro da Silva[2], Philippe Séguéla[2]
[1]McGill, [2]McGill University

Itch, or pruritus, can be described as an unpleasant sensation that leads to scratching behavior or the desire to scratch. Due to high prevalence in numerous diseases and widespread occurrence as a side effect of many medications, itch has become a prevailing research topic in recent years. Despite significant structural and behavioral overlap of pruriception and nociception, the underlying neurophysiological basis of itch sensation and its relation to pain is still unclear. More specifically, the enigma of how the somatosensory system differentiates itch and pain sensations and triggers distinct fight or flight behaviors remains to be solved. To investigate such distinction, we designed studies on animals with selective expression of excitatory DREADD (hM3D) and/or Channel Rhodopsin (ChR2) on the surface and terminals of MrgprA3 neurons. These primary nociceptors constitute a subpopulation of C-fibers known to be specifically linked to itch (Han et al., 2013). Functionality of the actuators is validated in vitro using calcium imaging and electrophysiology. As expected, behavioral studies show that chemogenetic activation of these neurons evokes stereotypical itch behavior rather than pain responses. Surprisingly, optical activation of these neurons through ChR2 predominantly induces pain avoidance behaviors rather than scratching. Our results show that in vivo a single population of C-fibers

can convey itch sensation in certain conditions and pain in others. This calls for other models to explain how itch and pain are distinctly coded in the central nervous system.

3-D -159 Delayed Sox9 ablation in a mouse model of chronic spinal cord injury

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[1]Western University

The majority of individuals who have suffered from traumatic spinal cord injury (SCI) have longstanding damage leading to debilitating sensory and motor impairments. These impairments are due to the loss of functional neuronal connections that occurs in the spinal cord following trauma. The molecular environment of the spinal cord is not permissive to axonal growth and thus neuroplasticity after injury is limited. Perineuronal nets containing chondroitin sulfate proteoglycans (CSPGs) are extracellular matrix structures surrounding neurons and are known to be major inhibitors of axonal sprouting. Our laboratory has identified that the transcription factor SOX9 regulates a battery of genes involved in CSPG biosynthesis. Using Sox9 conditional knock-out mice, we have shown that ablating Sox9 just before injury decreases CSPG levels in the injured spinal cord, leads to improved locomotor recovery and increases neuroplasticity. However, it is not known whether delayed ablation of Sox9 following spinal cord injury leads to similar recovery. To investigate this question, Sox9 was ablated in mice 3 weeks post-spinal cord injury. Levels of perineuronal net matrix, neuroplasticity, and locomotor recovery will be presented.

3-D -160 The Role of Network Connectivity in the Speed of Neural Synchronization

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Synchronization in neural networks has received much attention due to its role in epilepsy, memory consolidation and temporal coding in general. While most research has focused on the conditions under which a network will synchronize or not, less work has explored the network features that determine the speed of synchronization. The medullary pacemaker nucleus of the weakly electric fish comprises a synchronized network of high-frequency neurons, weakly coupled via gap junctions. Levels of synchrony in the pacemaker are behaviourally modulated on millisecond time-scales, but how gap junctional connectivity enables this behaviour is still poorly understood. Here, we use a computational model of the pacemaker, along with graph theory analyses, to investigate how synchronization speed changes with network randomness and the directionality of coupling (bidirectional/non-rectifying versus directional/rectifying gap junctions). Our results lead to predictions about connectivity in the pacemaker nucleus and about information coding and propagation in neural networks more generally. Supported by an NSERC USRA to EW and an NSERC Discovery Grant to JEL.

3-D -161 Granulocyte-colony stimulating factor (G-CSF) mediates central sensitization underlying chronic visceral pain following inflammation

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[1]University of Calgary

While abdominal pain is the most common symptom of gastrointestinal disroders (inflammatory bowel disease (IBD)), the pathophysiological mechanisms involved in the sensitization of pain signaling pathways in IBD remain elusive. As a result of sensitization, about 30% of IBD patients in remission (without sign of inflammation) develop Irritable Bowel Syndrome (IBS)-like symptoms, including abdominal pain. It has been shown that mucosal inflammation leads to the reduction of the activation

threshold of peripheral sensory neurons, process called peripheral sensitization. On the other end, chronic pain states (nerve injury, arthritis) are also linked to central sensitization, phenomenon implying activation of cells in the central nervous system, including spinal cord neurons and microglia. Here, we examined the spinal mechanisms that lead to central sensitization in response to colonic injury. We found that cytokine GCSF and its receptor are increased in the spinal cord of colitis mice. We show that microglia, the resident macrophages of the spinal cord, express the GCSF receptor. Intrathecal injection of GCSF in mice induces visceral hypersensitivity, an effect that was abolished in animals depleted of microglia. In vitro, DRG neurons co-cultured with GCSF-conditioned BV2 microglial cells displays increased excitability measured by patch clamp electrophysiology. Finally, blocking GCSF intrathecally with anti-GCSFR antibody alleviates post-inflammatory visceral hypersensitivity induced by colitis. GCSF could thus represent a new target for the treatment of abdominal pain

3-D -162 Frontal eye fields (FEF) contributes differentially to collicular preparatory activity for short versus long latency saccade

Suryadeep Dash[1], Tyler Peel[1], Stephen Lomber[1], Brian Corneil[1]
[1]Western University

Premotor circuits in higher animals are complex, with multiple brain areas and pathways participating in preparation and execution of the movement. Consider for example the primate oculomotor system, and how activity is coordinated within FEF and iSC during the preparation and execution of a simple visually-guided saccade. Although the FEF has direct projections to the saccadic burst generator, its major influence on saccadic behaviour is thought to be exerted through the iSC. To understand the FEF's role in saccade preparation, we examined the level of low-frequency iSC preparatory activity during reversible inactivation of the FEF. As expected, FEF inactivation lowered the overall level of iSC activity related to saccade preparation, and produced behavioral changes by increasing saccadic reaction times (SRTs). However, SRTs made with and without FEF inactivation overlapped, enabling us to specifically compare, across FEF inactivation, the level of preparatory iSC activity preceding movements matched for SRT. We found two surprising results: 1. increased levels of iSC preparatory activity during FEF inactivation was observed only for saccades generated at SRTs exceeding ~170 ms; and 2. the profile of iSC preparatory activity before shorter SRTs, including the occasional express saccade, was unaltered during FEF inactivation. A closer look at the neural activity for longer SRTs revealed that higher preparatory activity preceding long SRTs was needed to compensate for reduced visual activity during FEF inactivation. Overall, our results suggest a latency-specific contributio

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3-D -163 An implicit approximate normalization model for multi-sensory integration across reference frames

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Many brain processes (including multisensory integration and reference frame transformations) can be performed by probabilistic inference (PI). Divisive normalization (requiring intractable integral) has been proposed as a possible mechanism for implementing PI in the brain. Here, we propose an alternative, more physiologically feasible, mechanism to perform divisive normalization; implicit approximate normalization (IAN). We implemented a multi-layer feed-forward neural network using different neural coding schemes within the same network and trained it to perform multisensory integration across reference frames in one step using a standard pseudo-Newton method with preconditioned conjugate gradient descent. The performance of this network was comparable to a probabilistic population code network, but without requiring non-linear/divisive operations. IAN produces a wide range of behaviors similar to recorded activity in the brain: inverse effectiveness, the spatial correspondence principle, gain-like modulations, super-additivity, multisensory suppression, and modulation of neural activity by varying cue reliability. The strength of IAN is that it performs well with a fraction of the units required by explicit methods (i.e. in a network with two cues to be combined in 3-D and 100 units in each dimension, divisive normalization requires 10^12 while IAN requires 10^3 units). In conclusion, the results of this study demonstrate that normalization can be done in simple feed-forward networks of purely additive units without the requirement of explicit divisive normalization.

3-D -164 Dopaminergic modulation of song preference in the female zebra finch

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Vocal communication signals are critical in social interactions across many species. In the zebra finch, a highly social songbird species, males produce learned vocal signals ('songs') during courtship interactions. Zebra finch females do not sing but attend to acoustic features of song; they exhibit preferences for particular song features and for the songs of certain males. However, the neural circuits involved in encoding song preferences remain unknown. Here, we investigated the role of catecholaminergic neurons and their projections to a secondary auditory region, the caudomedial nidopallium (NCM), in female song preferences. We found that dopaminergic neurons in the ventral tegmental area (VTA), but not other midbrain catecholaminergic neurons, showed greater immediate early gene expression in response to playback of courtship versus non-courtship song, an effect which parallels female preferences for courtship song. We then investigated whether changes in catecholaminergic activity could drive changes in preference through effects on the NCM. We first measured female responses to the songs of two males. We then paired passive exposure to the less preferred song with reverse dialysis of either dopamine or norepinephrine agonists into the NCM. Our findings suggest that pairing passive exposure to the less preferred song with stimulation of dopamine

receptors in the NCM can increase or even reverse song preferences. Together, these data indicate that midbrain dopaminergic activity may participate in encoding female song preference through effects on NCM.

3-D -165 Identification of cortical neurons active during stroke recovery

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Both clinical and preclinical studies have shown the remarkable innate ability of the brain to exhibit recovery from stroke, often termed spontaneous biological recovery. This recovery includes significant and rapid physical improvements that are limited to a critical sub-acute time window following a stroke. To harness and extend this recovery, it is critical to understand what underlies this phenomenon. Increasing evidence supports the idea that recovery stems from a remapping of cortical function. This includes the reallocation of functions that were previously under the control of the afflicted region to other regions, including the peri-infarct regions, as well as the non-affected contralateral hemisphere. However, it has been challenging to identify at the cellular level the new motor networks that arise, how they change over time, and to what extent they contribute to functional recovery. Using the Arc-CreERT2 transgenic mice, we have developed paradigms that are allowing us to determine what cells are part of the neural networks that is functionally active within the existing neuronal network spared by the stroke and when they are activated (before versus after stroke versus during recovery). Specifically, we can label neurons that are activated by a sensorimotor task either before or following a cortical stroke induced via photothrombosis. Identification of this network will lay the foundation for future studies in which these active networks will be stimulated in order to determine if the rate or extent of spontaneous recovery can be improved.

3-D -166 Neurophysiological basis of bilateral differences in manual forces in young and older adults

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In this study, we investigated the physiological basis of bilateral differences in manual forces in two groups of right-handed adults (young, n=12, senior, n=11). Manual forces were measured during unilateral and bilateral efforts (pinch and grip strength). In parallel, transcranial magnetic stimulation (TMS) was used to examine bilateral differences in corticomotor excitability and in transcallosal inhibition. Laterality indices were derived from both strength and TMS measures. During unilateral efforts, laterality indices were comparable for strength measures in the two age groups, indicating similar degrees of asymmetry with age. During bilateral efforts, bilateral indices, reflecting bilateral force deficit, were larger in seniors (-6.0±2%) than in young (-3.2 ±t 1.7%). For TMS measures, no differences in relation to age were found in indices of laterality for both corticomotor excitability and transcallosal inhibition measures. A correlation analysis indicated that the greater asymmetry in pinch strength was positively related to leftward asymmetry in transcallosal inhibition (r=0.48, p=0.02). In the young group, an inverse relationship was found between greater leftward asymmetry in corticomotor excitability and bilateral force deficit in hand grip strength. Altogether, these observations indicate that asymmetries in manual force production are not greater with age. In addition, our correlations indicate that leftward asymmetries in transcallosal inhibition are related to greater rightward asymmetries in pinch strength.

3-D -167 MR-based age- and sex-related effects on the striatum, globus pallidus and thalamus in healthy individuals across the adult lifespan

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While age-related changes are major risk factors in neurodegenerative diseases, there are limited studies investigating changes in subcortical morphology associated with healthy aging. Furthermore, since prevalence, onset age and symptomatology of many neuropsychiatric disorders differ between males and females, we examined the effect of age and sex, as well as motor performance on the volume of the striatum, globus pallidus and thalamus in healthy individuals. 91 healthy subjects underwent T1-weighted MR imaging (18-80 years old; Siemens 3T Trio; 1mm3). Images were segmented using MAGeTbrain to estimate the volume of the striatum, globus pallidus and thalamus. A general linear model was performed to examine the association between age, sex and their interaction, and subcortical volume. Total brain volume was used as a nuisance variable. A secondary analysis included performance on the grooved pegboard task in the model. Bilateral age-related volumetric decreases were observed in all three structures of interest ($p<0.01$). Sex-specific rates of bilateral striatal volumetric decline were observed; steeper rate of decline in females (left $p=0.03$;right $p=0.05$). Moreover, larger contralateral thalamic volume predicted higher grooved pegboard scores (left $p=0.05$;right $p=0.04$). These results expand knowledge of age-related changes in the healthy brain, suggesting a substantial modulation of sex on the rate of volumetric decline. Improved understanding of sex-specific trajectories across the lifespan can improve our understanding of sex differences in neuropsychiatric disorders.

E - Homeostatic and Neuroendocrine Systems

3-E -168 Glycemic state alters adropin responsiveness of rat paraventricular nucleus neurons

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Adropin is a peptide hormone that has been observed to have metabolic roles in the periphery, and a central role to inhibit water intake. We have recently shown that adropin directly influences the excitability of hypothalamic paraventricular nucleus (PVN) neurons. Here, using the whole-cell current-clamp technique in rat brain slices, we show that the responsiveness of PVN neurons to adropin is altered when the extracellular glucose concentration is reduced. In our original experiments at 10 mM glucose (central hyperglycemia), adropin (10 nM) elicited responses in 68% of cells tested (n=57/84). The majority of cells (58%) depolarized (5.2 ± 0.3 mV; n=49) in response to adropin, while the remaining responsive cells (10%) hyperpolarized (−3.4 ± 0.5 mV; n=8). Reducing the extracellular glucose concentration eliminated adropin-mediated hyperpolarizations. In 3 mM glucose (central normoglycemia), adropin (10 nM) elicited responses in 47% of cells tested (n=7/15), all of which were depolarizations (4.8 ± 0.5 mV). In 1 mM extracellular glucose (central hypoglycemia), 10 nM adropin elicited depolarizations in 67% of cells tested (6.0 ± 0.8 mV; n=8/12), while the remaining 33% of neurons (n=4) did not respond to adropin application. The magnitudes of depolarizations were not different at each glucose concentration (p=0.50). These findings demonstrate that the glucose environment affects adropin-mediated responses in PVN neurons and reveal the importance of considering glycemic state when studying molecules or pathways pertaining to the central regulation of energy homeostasis.

3-E -169 Characterization of Prolactin Action in the Subfornical Organ

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The subfornical organ (SFO) is a region of the brain lacking a lipophilic blood-brain barrier and is therefore primed to respond to circulating peptide signals. The SFO has been classically implicated in energy and fluid homeostasis but has the potential to influence estrous cyclicity and gonadotropin release. Prolactin (PRL), a peptide hormone, has also been shown to influence these aspects of reproduction. Using real-time quantitative PCR, we identified PRL receptor mRNA in the SFO in Sprague Dawley rats. PRL receptor expression does not significantly differ between males (n=10) and females (n=24), between juveniles (n=10) and adults (n=24), or across the estrous cycle (n=19). Patch-clamp recordings were then obtained in juvenile male rats to further investigate the actions of PRL at the SFO. Dissociated SFO neurons perfused with 1µM PRL resulted in 45% of neurons depolarizing, 14% hyperpolarizing, and 41% not responding in the current-clamp configuration (n=23). Preliminary data suggests that the proportion of responders increase at decreased concentrations of PRL. Preliminary voltage-clamp experiments also suggest that PRL may depolarize neurons by inhibiting transient potassium channel function. Together, these data suggest potential functional roles for prolactin at the SFO, although further studies will be required to elucidate the reproductive/homeostatic functions of PRL at this circumventricular organ.

3-E -170 Depression as a Gut Feeling: The role of the gut microbiome in the link between early life stress, inflammation, and adult depression

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A growing body of preclinical research has recently expanded the conventional view of gut bacteria from a requisite digestive aid to an important modulator of almost every major system in the body, including the stress response, the immune system, and the brain. This paradigm shift has led to an increased interest in the gut microbiome as a mediating factor in the development of major psychopathologies, such as depression, and a possible target for future interventions. It is well established that early stress and neural inflammation are risk factors in the onset of depression and that the gut microbiome indeed interacts with these systems. However, a direct link between stress-induced gut microbiome dysregulation and depression has yet to be established. Our objective was to first characterize the behavioural and neurobiological effects of cumulative early life stress on male and female C57BL/6J mice. We assessed the effects of limited bedding and/or maternal separation on offspring corticosterone reactivity, inflammation, anxiety and depressive-like behaviours, and gut dysbiosis. These preliminary data validating the sex-specific effects of early life stress on adult mouse behaviour and gut-brain neurophysiology will allow us to investigate the role of the gut microbiome in mediating the effects of early life stress on depression vulnerability, as well as translate these findings to humans using postmortem tissues from depressed suicides.

3-E -171 The Changes in Mean Platelet Volume after Using Antiplatelet Drugs in Acute Ischemic Stroke: A Randomized Controlled Trial

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BACKGROUND: Larger platelets are more reactive than smaller ones due to their greater content in granules, mean platelet volume (MPV) values have been found in patients with stroke than in controls. OBJECTIVE: To measure the changes of MPV after using four antiplatelet drugs in patients with acute non-cardioembolic ischemic stroke and assess the association of antiplatelets and MPV and stroke outcome. MATERIAL AND METHOD: Ischemic stroke survivors were randomly allocated into four groups, receiving aspirin, clopidogrel, combined aspirin/dipyridamole, and cilostazol. The change of MPV, national institute of health stroke scale (NIHSS), and modified Rankin Scale (mRS) were recorded at baseline and 4th-week in all studied groups. Mean platelet volume was measured using the standard automated blood test form complete blood count. RESULTS: Twenty-one subjects were included. They comprised of five cases in each antiplatelet group, except six patients in the aspirin group. Male was 57%, and hypertension was the commonest risk factor (61.9%). Most of participants (76%) had small vessel disease. At the 4th-week, MPV was reduced and NIHSS and mRS were improved in all studied groups. Clopidogrel significantly reduced NIHSS ($p = 0.003$), and it produced the greatest reduction in MPV compared to others. CONCLUSION: Every type of antiplatelets included in this study reduced mean platelet volume, NIHSS, and mRS in patients with acute non-cardioembolic ischemic stroke. Compared to others, clopidogrel showed the greatest reduction in MPV and the most improvement on stroke outcome.

3-E -173 Salt loading promotes synchronization of vasopressin neurons in the supraoptic nucleus

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The antidiuretic hormone vasopressin (VP) is released from magnocellular neurosecretory cells located in the hypothalamic paraventricular and supraoptic nuclei (SON). Vasopressin neurons sense variations in extracellular fluid osmolality and adapt their firing rate proportionally. Under hyperosmotic conditions the electrical activity changes from silent to progressively higher firing rates and ultimately to a type of bursting pattern named "phasic", where groups of spikes are interspersed by silent pauses to facilitate VP release (Poulain & Wakerley, 1982). In acute hypertonic conditions in vivo, spontaneous phasic activity is asynchronous among VP cells. Interestingly, another type of bursting can be observed in VP cells with a briefer and high frequency spiking activity called clustering which can be induced by NMDA receptor activation (Gagnon et al., 2014). However, it remains unknown whether clustering is synchronous or asynchronous between VP neurons. Paired extracellular recordings in superfused hypothalamic explants confirmed that phasic firing is asynchronous between VP cells. However recordings from SON neurons in explants prepared from salt loaded rats displayed a high degree of synchronization between bursts. The basis for this effect remains to be determined. However it is interesting to note that this condition induces a pronounced retraction of astrocytic processes in the SON. Future experiments will test this hypothesis.

3-E -174 Antibiotic treatment prevents stress-induced plasticity

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A threat to survival triggers a defense mechanism called the stress response. This response is initiated by corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus (PVN) of the hypothalamus. Recent studies demonstrate that manipulation of the gut microbiome affects the behavioural response to stress. However, the mechanisms by which gut flora affects the stress response is not clear. Here we investigated whether a brief, antibiotic-induced disturbance of gut flora affects

synaptic transmission and homecage behavior following stress. An antibiotic cocktail (neomycin, vancomycin, ampicillin) was administered in the drinking water for 7 days. On day 7, coronal brain slices were prepared for electrophysiological experiments. To examine the effects of antibiotics on the neural response to stress, one littermate was removed from the cage and exposed to a stressor for 5 min (10 footshocks, 0.5mA). Antibiotic treatment did not change basal synaptic properties of CRH neurons. Consistent with previous findings, exposure to a single acute stress allowed glutamate synapses to undergo short-term potentiation following a burst of high frequency afferent activity. Antibiotic-treated mice showed no short-term plasticity. In addition, antibiotic-treated mice showed differences in homecage behavior after stress. Immediately after stress, water-treated mice exhibited ano-genital sniffing of their cagemate. This behavior was reduced in antibiotic-treated mice. These results suggest that antibiotic treatment disrupts the normal behavioural and neural response to stress.

F – Cognition and Behavior

3-F -175 Phasic optogenetic stimulation of mesolimbic dopaminergic terminals in the nucleus accumbens reinforces the value of a goal-directed action in operant conditioning

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Nucleus accumbens (NAc) dopamine is involved in various aspects of reward seeking behavior, including instrumental/reward-related learning, behavioral activation and motivation (i.e. willingness to exert effort). Yet, the specifics of this contribution are highly complex and have thus far been difficult to disentangle. Here, we optogenetically interrogated the mesolimbic dopaminergic projection, originating from the ventral tegmental area (VTA) and projecting to the NAc. To study the effect of the activation of the VTA-NAc dopaminergic projections, we expressed ChR2 in the VTA of DAT-Cre mice and optogenetically stimulated the DA terminals in the NAc using stimulation parameters that mimic physiological phasic discharge of DA neurons. We show that phasic activation is sufficient for self-stimulation in an operant conditioning task. Yet, as shown by real-time place preference, the same phasic activation of this pathway is not rewarding by itself. To dissect reward processing from motivational features, we combined a self-stimulation operant conditioning set-up with a possibility of obtaining the same optogenetic stimulation by refraining themselves from lever pressing. Using this novel paradigm, we show that animals continue to lever press for optogenetic stimulation of the VTADA-NAc, instead of opting for the "effort-free" stimulation, suggesting the specific involvement of this pathway in the reinforcement of goal-directed actions. Together, our data support the hypothesis that one effect of phasic mesolimbic DA is to reinforce the value of a goal-directed action.

3-F -176 Implications of the translational repressors 4E-BP1 and 4E-BP2 in sleep architecture and EEG activity

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Introduction: Studies support an implication of synaptic proteins in sleep regulation but little is known about the role of the protein synthesis machinery. 4E-BP1 and 4E-BP2 are translational repressors inhibited by mTORC1 phosphorylation. 4E-BP1 is highly expressed in the suprachiasmatic nucleus and has roles in circadian rhythms. 4E-BP2, widely expressed in the brain, is critical for memory and plasticity. 4E-BP2 knockout (KO) mice exhibit autistic behaviors. Yet, there is no data on their implication

in sleep regulation. Thus, the aim of this study is to verify the contribution of 4E-BP1 and 4E-BP2 in sleep regulation. Methods: Wild-type (WT), 4E-BP1 and 4E-BP2 KO mice were implanted with electroencephalography (EEG) and electromyography (EMG) electrodes and recorded continuously for 48 h starting with a 24-h baseline followed by a 6-h sleep deprivation (SD). Behavioral states were assessed based on the EEG/EMG traces. Changes in mRNA expression after SD in the cerebral cortex were measured by qPCR. Results: 4E-BP1 KO mice exhibit less wakefulness and delta EEG activity only during baseline, without changes in sleep fragmentation. Analyses for 4E-BP2 KO mice and of the gene expression response to SD are underway. Because 4E-BP2 is more expressed in the brain, a stronger phenotype is expected. Conclusion: Our findings support a role for the protein synthesis machinery in the regulation of sleep and wakefulness. More precisely, our results indicate that the translational repressor 4E-BP1 regulates vigilance state duration and EEG activity.

3-F -177 Functional cognitive reserve is related to enhanced activity of adult-born dentate granule neurons

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Early-age running enhances survival of adult-born hippocampal neurons later in life. This effect may be a contributing factor to the neurogenic reserve (NR) that serves as a buffer and protects the brain against age-related cognitive decline. Normal aging is often associated with hippocampus-related memory decline but is accelerated in pathological cases. Memory precision in terms of discrimination between specific and novel contexts is dependent on the optimal functioning of the hippocampus. To test if NR serves as a mechanism to improve memory one group of juvenile rats was given free access to running wheels for 6 weeks and another group was housed in standard laboratory cages. Then, the runners were returned to standard cages. After 4 months rats were trained on a contextual fear (CF) conditioning task and, 2 weeks later, tested for memory of the CF response. The testing was done on the same context as well as similar and very different contexts to provide information on the quality of memories. Using immunohistochemical methods with a mitotic marker CldU and an activity marker c-Fos we demonstrated the enhanced activity of adult-born dentate granule neurons in comparison to developmentally-born neurons. The activity of adult-born granule neurons during memory retrieval was increased by early age running. The memory of association with the specific environment was also enhanced. Our findings emphasize the involvement of adult-born hippocampal neurons in neurogenic and functional cognitive reserve and show that physical activity contributes to memory improvement.

3-F -178 Cholinergic agonist carbachol increases delay activity and reduces task selectivity in macaque prefrontal cortex

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The dorsolateral prefrontal cortex (DLPFC) subserves multiple cognitive processes including working memory and representation of abstract rules. The cholinergic system, which acts upon nicotinic and muscarinic receptors, is involved in the modulation of working memory, and removal of this innervation to prefrontal cortex results in decreased working memory performance. Local cholinergic modulation of rule-contingent mnemonic processing in DLPFC has not been examined in detail hitherto. We have previously shown that the muscarinic antagonist scopolamine suppresses activity and rule selectivity in prefrontal neurons. In this study, we examined the effects of iontophoretically applied nonspecific cholinergic agonist carbachol to DLPFC neurons of rhesus macaque monkeys as they perform a rule-memory pro- and anti-saccade task. Two macaque monkeys (Macaca mulatta) must remember a brief

colour-cued rule over a delay period. The subjects will then make an eye movement towards (pro-saccade) or away from (anti-saccade) a peripheral stimulus, depending on the previously presented colour-cued rule. Upon application of carbachol, we observed both excitation and inhibition of prefrontal neurons. Out of 84 neurons, two-way ANOVA revealed 31 neurons with main effect of rule-type (i.e., higher delay epoch activity for pro- vs. anti-saccade), 68 showed main effect of drug condition, and 10 showed interaction of rule-type and drug condition. Further, preliminary results suggest that cholinergic stimulation via carbachol both augmented and attenuated rule selectivity in rhesus DLPFC.

3-F -179 Optogenetic activation of the infralimbic cortex inhibits context-induced renewal of Pavlovian sucrose-seeking

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The objective of the present research was to examine the role of the infralimbic medial prefrontal cortex (IL) in the suppression of appetitive conditioned responding after extinction. Specifically, we used in vivo optogenetics to activate the IL during conditioned stimulus (CS) trials in an appetitive, Pavlovian context-induced renewal test. Male, Long-Evans rats received microinfusions of a virus containing channelrhodopsin frame-fused with enhanced yellow fluorescent protein (ChR2-eYFP) or eYFP alone (0.5 µl, unilateral), and an optical fiber implant targeting the IL (AP +2.9; ML +/-0.6; DV -5.1). Rats were trained on Pavlovian conditioning in a distinct context (Context A) in which CS trials (10 s white noise) were paired with 10% sucrose (0.2 mL per CS trial, 14 trials per session). Next, rats underwent extinction in a different context (Context B) in which CS trials occurred without sucrose. Finally, rats were tested for context-induced renewal of sucrose-seeking in Context A. At test, CS trials co-occurred with laser activation (473 nm, 20 Hz, 5 ms pulse) in the absence of sucrose. Optical stimulation of the IL during CS trials significantly reduced renewal in rats that expressed ChR2, but not in eYFP controls. These results suggest that activity in the IL suppresses appetitive conditioned responding after extinction, and that this effect may be time-locked to the CS. Ongoing studies are testing the effect of optical IL stimulation during inter-trial intervals on renewal, and the role of projections from the IL to the nucleus accumbens shell on renewal.

3-F -180 NCK1 Knockout Mice Display Anxiety-like Behaviour and Memory Impairments

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Advances in genomics and proteomics have given us new insights into psychiatric disorders. Genome-wide association studies have implicated a number of genes involved in actin polymerization in a variety of psychiatric disorder including schizophrenia, bipolar disorder, Alzheimer's disease, intellectual disabilities, and autism spectrum disorders. Here we examine the function of NCK1, an intracellular scaffolding protein implicated in schizophrenia and known to play a role in actin dynamics, in the mouse brain and behavior. We show that NCK1 is found in neurons throughout the adult mouse brain with high expression levels in areas associated with learning, memory, and anxiety. Mice lacking NCK1 show increased levels of anxiety in an elevated plus maze and impairments in learning, short term and working memory in the Morris water maze, social recognition task, and Y-maze; however, no defects in neuronal proliferation or migration were seen in these mice. Examination of brain centers important for anxiety and memory, including the lateral amygdala, revealed that although there were no gross changes in overall size, we found differences in the morphology of synapses between control and mutant mice. Together, these results support a role for NCK1 in normal behavior and implicate a defect in synapse development or maturation in these events.

3-F -181 Adiponectin is required for physical exercise to restore hippocampal neurogenesis in streptozotocin-induced diabetic mice

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Diabetes is associated with impairment in cognitive functions. Animal studies using streptozotocin (STZ)-induced diabetic model has demonstrated that behavioral deficits in learning and memory task is associated with the loss of adult hippocampal neurogenesis. Exercise training is effective in counteracting diabete, and enhancing learning and memory performance, and promoting adult hippocampal neurogenesis. Adiponectin (an adipocyte secreted hormone) is a key mediator for exercise-enhanced hippocampal neurogenesis. Obese/diabetic patients display a significant decrease in the blood levels of adiponectin, which can be reserved by exercise training. Therefore, we hypothesized that adiponectin mediates the counteractive effect of exercise on diabetic-suppressed hippocampal neurogenesis. Using STZ-induced diabetic in wildtype or adiponectin knockout (adipo-/-) mice with/without voluntary running, we reported that diabetic non-exercised mice displayed significant decrease in hippocampal adiponectin levels and increase in blood corticosterone levels. Immunostaining data indicated that non-exercised diabetic wildtype mice showed significant decrease in cell proliferation, survival and neuronal differentiation. Two-week running restored the decrease in neurogenesis in diabetic wildtype mice, but not in diabetic adipo-/- mice, indicating that adiponectin is indispensable for physical exercise-promoted hippocampal neurogenesis. The results suggested that adiponectin could be a therapeutic target for treatment learning and memory impairment associated with diabetes.

3-F -182 Resting State Connectivity of Striatum and Midbrain Nuclei: Relation to Impulsivity, Sensation-Seeking and Body Weight

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High levels of trait impulsivity (IMP) and sensation-seeking (SS) are common features of adolescence and believed to be related to the ongoing development of fronto-subcortical circuitry. However, while these traits increase within subjects during adolescence, they also vary between subjects. Since high levels of IMP and SS are associated with an increased risk for obesity, this study examined correlations between the connectivity of nuclei in the basal ganglia and dopaminergic midbrain with body weight, and measures of IMP and SS in a population of young adolescents. Resting state fMRI data were collected for 116 children between the ages of 12 and 14. Connectivity with regions of interest in the left and right sub-thalamic nucleus (STN), ventral striatum (VS), ventral tegmental area (VTA) and substantia nigra (SN), was correlated with body mass index (Z-Scored for age) and IMP and SS scores from the Substance Use Risk Profile Scale. IMP was positively correlated with the connectivity between the left VS and the ventromedial prefrontal cortex, and the left STN and temporal and parietal regions. SS was negatively correlated with the connectivity between the left and right VTA and the anterior cingulate cortex and temporoparietal-junction. BMI Z-Score for age was positively correlated with the connectivity between the right SN and left STN and the entorhinal cortex, the left and right STN and the parahippocampal gyrus, and the left VTA and the cerebellum. This may reflect differences in networks regulating decision-making and food choices associated with these traits.

3-F -183 THE EFFECTS OF INTERMITTENT THETA-BURST STIMULATION ON WORKING MEMORY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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People with depression often struggle with a battery of debilitating cognitive impairments like decreased working memory. The brain areas associated with cognition, such as the prefrontal cortex and hippocampus are negatively affected by depression; studies have shown decreased volume, activity, and disturbed brain connectivity in those two areas. Currently, there is a lack of treatment options for improving working memory in depressed patients. Therefore, we focussed on exploring the therapeutic potential of an emerging treatment called intermittent theta-burst stimulation (iTBS). iTBS has been shown to be effective in treating mood disturbances, and increasing plasticity and inducing neurogenesis in patients. These findings suggest a potential for iTBS as a therapeutic treatment for working memory in depressed patients. We recruited 10 patients with major depressive disorder (MDD) and they received the standard 25 days of iTBS treatment. We used the n-back task, with conditions 0 and 2 back during a functional magnetic resonance imaging (fMRI) scan to test participants' working memory. Participants completed a scan before and after their full iTBS treatment. We hypothesize that the MDD group will perform significantly better on the n-back task after the iTBS treatment, and show significant changes in functional connectivity and resting-state activity for the prefrontal cortex and the hippocampus. Our pilot study aims to provide evidence for iTBS as a valuable treatment tool for working memory, and to gain new insights into some of the mechanisms behind the effects.

3-F -184 CONTINUOUS D-AMPHETAMINE TREATMENT DURING INTERMITTENT COCAINE SELF-ADMINISTRATION ATTENUATES INCENTIVE MOTIVATION FOR COCAINE AND COCAINE-INDUCED REINSTATEMENT OF DRUG SEEKING

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Cocaine addicts are thought to consume the drug intermittently within a bout of intoxication, presumably producing spikes and troughs in brain drug levels (Beveridge et al., 2012). To model this in rats, during a 5-6h self-administration session, cocaine is available during 5-min periods intercalated with 25-min no-drug periods. This produces spiking brain cocaine levels, increases motivation for the drug (Zimmer et al., 2012) and sensitizes the dopamine transporter (Calipari et al., 2013). One hypothesis is that these changes are due to neuroplasticity evoked by spiking brain levels of monoamines, in particular dopamine. If this is true, then flattening and/or widening monoamine spikes should reduce incentive motivation for cocaine. To test this here, rats self-administered cocaine during 14 IntA-sessions. One group concomitantly received D-amphetamine via a s.c. osmotic minipump. This increases monoaminergic tone, thus presumably changing the kinetics of cocaine-induced monoamine spikes. Next, we measured the motivation to take cocaine under a progressive ratio schedule of reinforcement, and cocaine-induced reinstatement of drug seeking behavior. D-amphetamine treatment attenuated the later motivation for cocaine. D-amphetamine treatment also reduced cocaine-induced reinstatement of cocaine seeking ~3 weeks after the last IntA-session, indicating long-term changes in the susceptibility to reinstatement. Thus, continuous D-amphetamine treatment during cocaine intake could be a promising perspective to treat cocaine addiction.

3-F -185 Characterizing the neural networks supporting conceptually and spatially guided retrieval of autobiographical memories

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Autobiographical memories (AMs) can be remembered differently, yet how these differences are reflected in the brain is unclear. Evidence suggests that the hippocampus, a structure located within the medial temporal lobes (MTL) and critical for recalling memories, distinguishes between types of memory retrieval. Further, anatomical evidence shows that hippocampal sub-regions each project to distinct networks of brain regions. Here, we characterized the neural networks that support different forms of remembering by comparing neural activity for remembering conceptual and spatial details from retrieved and newly accessed memories. In a MRI scanner, 24 participants completed experimental trials that began with remembering a pre-selected AM. Next, participants focused on either the thematic (conceptual condition) or spatial (spatial condition) elements of that memory. Finally, they used the recovered details to access and elaborate on a new memory. For both conditions, accessing details from an already-recovered memory depended more on posterior brain regions (posterior MTL, precuneus) whereas accessing details of a new memory depended more on anterior brain regions (anterior MTL, lateral temporal lobes). Comparing conditions, anterior temporal lobe regions were more robustly recruited for the conceptual condition and posterior hippocampal and parietal regions for the spatial condition. These data provide insight on the neural organization of AMs and inform our understanding of the mechanisms of memory.

3-F -186 Chemogenetic silencing of midbrain dopamine neurons and their projections to the nucleus accumbens core attenuates Pavlovian alcohol-seeking behaviour

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We examined the role of dopamine receptors, midbrain dopamine neurons and dopaminergic projections to the nucleus accumbens core (NAcC) in alcohol-seeking elicited by a Pavlovian, alcohol-predictive cue. Male, Long-Evans rats (Envigo) received 15% ethanol (EtOH) in the home-cage, followed by Pavlovian conditioning sessions in which a 10 s conditioned stimulus (CS; 15/session) was paired with EtOH (0.2 ml/CS, 3 ml/session). At test the CS was presented without EtOH and entries into the fluid port during the CS were assessed. Systemic eticlopride (D2/3 receptor antagonist; 10 µg/kg), but not SCH 23390 (D1-like receptor antagonist; 10 µg/kg) attenuated alcohol-seeking elicited by the CS. Next, we used chemogenetics to determine if midbrain dopamine neurons and their projections to NAcC were needed for alcohol-seeking. Male, transgenic TH::Cre rats received microinfusions (1 µl/side) of a cre-dependent viral vector encoding the Gi-Coupled (hM4Di) designer receptor into the ventral tegmental area (VTA). This receptor induces neuronal silencing when bound by clozapine-n-oxide (CNO). Behavioural training was as described above. At test, alcohol-seeking elicited by the CS was significantly attenuated by systemic CNO (Exp 2; 0, 10 or 20 mg/kg i.p.) or by CNO microinfusions into the NAcC (Exp 3; 0 or 3 mM, 0.3 µl/side). These data support the hypothesis that alcohol-seeking elicited by Pavlovian cues requires dopaminergic neurotransmission in the NAcC. Preliminary data indicate that dopamine in the NAc shell is needed for alcohol-seeking elicited by an alcohol-associated context.

3-F -187 Calcium imaging of medial septal glutamatergic neurons in freely-behaving mice

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Medial septal neuronal population are GABAergic, glutamatergic and cholinergic. The medial septum is known for modulating the activity in the hippocampal formation, but the contribution of glutamatergic neurons remain poorly understood. More specifically the spontaneous activity pattern of this neuronal

populations during behavior has not been well characterized as recording identified neuronal subpopulation in vivo in freely-moving mice is challenging. Using calcium imaging, our objective is to characterize the spontaneous activity of glutamatergic neurons during various behavior in freely moving mice. VGLUT2-Cre mice were injected with 0.5µl of the Cre-dependent AAV2/9-Syn-Flex-GcAMP6f virus. Three weeks later, mice were implanted with a chronic imaging device and subjected to different behavioral tasks. The activity pattern of glutamatergic neurons from the medial septum appeared highly specific to different behavioral aspects of the task. More specifically, the glutamatergic neurons elicited a locomotion-related activity suggesting a possible involvement in trajectory planning. Those results suggest that medial septum glutamatergic neurons contribute to hippocampal-dependent cognition.

3-F -188 The effect of norepinephrine release on odor discrimination learning in adult rats

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The locus coeruleus (LC) is the main source of norepinephrine (NE) in the brain with extensive projections throughout the cortex including the olfactory bulb (OB) and piriform cortex (PC). It has been shown that noradrenergic receptor blockade in either OB or PC impairs similar odor discrimination. The goal of this project is to test whether enhancing LC NE release using optogenetics promotes odor discrimination learning. Adult TH-CRE rats were bilaterally infused with adeno-associated virus containing light-excitable channels targeting noradrenergic neurons in the LC (AAV8-DIO-p2A-ChR2-EYFP). In vivo electrophysiology revealed LC neurons transfected with ChR2 virus are optimally active when blue light (473 nm) is given at a frequency of 10 Hz using 30 msec pulses of 93 mW through a 400 µm optic fiber. We are now determining the influence of two patterns of light (10 Hz, 10 sec on/20 sec off; and 3 Hz tonic) on the ability of rats to solve a difficult (highly similar) odor discrimination problem. Food deprived animals were first trained to discriminate between two simple odors, one paired with a food reward. Three weeks following virus infusion, animals were implanted bilaterally with an optical fiber to the dorsal LC. Rats are now undergoing a difficult odor discrimination in which animals are optogenetically stimulated with blue laser light. The number of trials required to reach successful learning criterion is assessed. This experiment will shed light on the role of norepinephrine release from LC on odor discrimination learning.

3-F -189 Susceptibility to chronic social defeat is related to increased hippocampal engram cells in the CA1 region

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Apart from mood changes, depression has been associated with biased memory for negative stimuli. Imaging studies suggest this cognitive bias is related to the enhanced functioning of the hippocampus. We hypothesize that the facilitated formation of hippocampal engram cells, cellular substrates for memory, is related to the cognitive bias for negative stimuli in depression. We employ a chronic social defeat model to examine the relationship between hippocampal engram cells and depression-related behaviours. The TetTag mouse model allows the tagging of activated neurons by a reporter gene LacZ. TetTag mice were stressed by social defeat, consisting of attacks by and co-housing with an aggressive mouse. After 8 days of social defeat, mice were separated into susceptible (exhibiting social avoidance) and resilient groups according to their social behaviour. Engram cells are reactivated by an extra episode of social defeat to induce cFos expression. Neurons with both LacZ and cFos labeling represent engram cells. We found more LacZ labeled hippocampal CA1 neurons in susceptible mice compared with resilient and nonstressed control mice. Such group difference was gone when we separately compared

data from the dorsal and ventral hippocampus. Intriguingly, we found significantly more engram cells in susceptible mice than other mouse groups in both the dorsal and ventral hippocampus. No difference in LacZ labeled and engram cells was found in the dentate gyrus. Our findings suggest susceptible mice may have an enhanced hippocampal memory for social stress.

3-F -190 The flexibility of combined attention: An examination of manual and oculomotor responses.

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Previous research demonstrates large effects on behavior when multiple attentional systems are engaged towards processing of the same target, relative to when a single attentional system is engaged in isolation. however, this so-called 'combined attention' effect has thus far only been demonstrated in manual performance without controlling for oculomotor influences. As such, it remains unknown if and whether combined attention may manifest when oculomotor performance is measured. To address this question, participants' automated, endogenous, and combined (automated and endogenous) attention orienting effects were measured. In separate sessions, they were asked to perform manual target detection while withholding eye movements and oculomotor target detection by looking at the target while withholding manual responses. Combined attention emerged in a similar fashion across manual and oculomotor response modalities, demonstrating the flexibility of the attentional systems' joint influence on human behavior.

3-F -191 Investigation of the Roles of Ndel1 in the Postnatal Hippocampus

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Ndel1 is a microtubule(MT)-associated protein recognized as an integrator of the cytoskeleton. The Nguyen lab created conditional knockout mice for Ndel1 in CA1 hippocampal excitatory neurons 1 month post birth. We found that Ndel1 CKO animals exhibit MT fragmentation in CA1 pyramidal neurons associated with dispersion and synaptic/dendritic pathology, as well as spatial memory impairment. Also, supplementation of secreted glycoprotein Reelin reduces MT fragmentation in CA1 pyramidal neurons as well as synaptic/dendritic pathology. I first asked whether memory deficits are caused by pyramidal cell death. Using immunostaining with neuron-specific marker NeuN, and CA1 specific marker Wfs1, I used stereological methods to quantify cells. Ultimately, neuronal survival was unaffected in the CA1. I found an upregulation of Lis1 and Dynein (2 binding partners & regulators of Ndel1) in Ndel1 CKO hippocampi. As overexpression of Lis1 in the brief presence of the MT destabilization agent nocodazole generates fragments of MTs disconnected from the centrosomes (Smith et al, Nat Cell Biol 2000), I reasoned that MTs fragmentation in CA1 pyramidal neurons of Ndel1 CKO mice involves increased Lis1 dosage. Lastly, I found that a single injection of Reelin reduces CA1 cell dispersion and improves the spatial memory of Ndel1 CKO mice during the Morris Water Task. In sum, my results indicate that MT fragmentation associated with increased Lis1 in CA1 pyramidal neurons contribute to spatial learning deficits of Ndel1 CKO mice, which can be ameliorated with Reelin supplementation.

3-F -192 Paying Attention to Normal Aging and Cardiovascular Risk Factors on Cognitive Variability.

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With an aging population, there is an increasing pressure for earlier detection of cognitive impairments due to neurological disorders. The presence of cardiovascular risk factors in older adults affects white matter tracts implicated in fronto-parietal attentional control networks, and also increases the likelihood of later developing dementia. Current gold-standard cognitive tests do not map well onto contemporary models of cognitive control, and may not be sufficiently sensitive to detect subtle cognitive decline due to poor cardiovascular health. Recent evidence in patients with early-stage Alzheimer's disease suggests reaction time intra-individual variability (RT-IIV) may be very sensitive to subtle attentional control deficits. However, no studies to date have examined whether attentional control tests are sensitive to cognitive decline due to aging and cardiovascular risk factors. To this end, healthy younger adults, healthy older adults, and older adults with cardiovascular risk factors were given the Local-Global task, Posner spatial cueing task, Flanker task, and cognitive functioning questionnaires. Aging was generally associated with longer mean RTs. Regarding accuracy and RT-IIV, the picture was more complex, with group differences depending on the task and metric. The results suggest that experimental cognitive control tasks have potential utility as clinical tools in the earlier detection of cognitive impairment due to the subtle effects of poor cardiovascular health on the brain.

3-F -193 Oscillatory representation of olfactory associations during episodic memory encoding in humans

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Changes in patterns of rhythmic neuronal activity during odor perception and learning remain largely unknown in humans. Only three studies have explored olfactory perception using electrophysiology, revealing odor-evoked potentials (OEP) in the amygdala and amplitude changes in beta and low gamma bands (Hudry et al., 2001, 2003; Jung et al., 2006). In this study, we aimed at characterizing oscillatory representation of odors during associative encoding using distributed multi-site intracerebral EEG recordings and machine-learning techniques. Seven surgical epilepsy patients took part of the experiment during which they freely encoded 8 olfactory-visuospatial associations. They explored on average 7.17 (± 3.62) times each association. Functionally, preliminary results revealed significant OEP and power modulations in θ, α, β and γ frequency bands during encoding in distributed brain regions such as the amygdala, the hippocampus, the insula, the middle frontal and temporal gyri, the fusiform gyrus and the angular gyrus. We also revealed that spectral power change was able to significantly decode encoding and resting oscillatory patterns. These results provided the first evidence for the role of OEP and band-specific power modulations during associative encoding in olfactory, visual imagery and memory brain regions. Further analyses are needed to fully characterize the contributions and interactions of these regions during associative encoding.

3-F -194 Episodic-like memory and Arc expression in Goto-Kakizaki rats

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Diabetes mellitus is a common metabolic disorder that has steadily increased in prevalence over the past five decades. Although type I and type II diabetes differ in their pathophysiology, both types are characterized by hyperglycemia, and both types have been associated with cognitive decline and increased risk of dementia. To further investigate the link between chronic hyperglycemia and cognitive

ability, here we test both memory performance and hippocampal function in the Goto-Kakizaki (GK) rat, which is selectively bred to have persistent hyperglycemia in the absence of obesity. Preliminary data indicate that GK rats show deficits, relative to Wistar rats of the same age, in performance of a what-where-when test of episodic-like memory. Further testing is being conducted to determine if the pattern of expression of Arc (an immediate-early gene critical for memory function) is altered in the hippocampus of GK rats during the completion of this task, or following spatial navigation. Analysis will focus on the dentate gyrus as the most likely brain region to mediate performance in a task with high-interference stimuli. Results of these tests will help to functionally link persistent hyperglycemia to changes in hippocampal physiology.

3-F -195 Long-term effects of adolescent chronic stress on TBI cognitive and emotional impairments in adult male rats

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Exposure to early life stress has lasting effects on behavior and brain function due to dynamic plasticity occurring in the developing adolescent brain. However, it is yet to be determined how stress exposure in this developmental period influences functional recovery post traumatic brain injury (TBI) later in life. Thus, the goal of this study was to test the hypothesis that stress in adolescence would confer deleterious effects on behavioral impairments post TBI in adulthood. Adolescent male Sprague-Dawley rats (n=40) were exposed to 4 weeks (postnatal day, PND, 30-60) of chronic unpredictable stressors (CUS) or no stress, and after a 1-month resting period (PND 60-90), were anesthetized and received a cortical impact of moderate severity (2.8 mm tissue deformation at 4m/s) or sham injury. After one week of recovery, anxiety-like behavior in the open field test (OFT), anhedonia in the sucrose preference test (SPT), and cognitive performance in the Morris water maze (MWM) were measured, and the brains collected 25 days post TBI for histological analysis. Preliminary results show increased entry in the center zone in the OFT, decreased sucrose consumption in the SPT, and reduced time to reach the platform in the MWM for CUS groups compared to no-stress groups, although TBI rats remained significantly more impaired in the MWM, and showed reduced emotional phenotype compared to sham controls. These results suggest that aversive environmental conditions in adolescence induce adaptive behavioral responses in TBI rats, albeit, without leading to full functional recovery.

3-F -196 The neurobiology underlying partially observable Markov decision processes

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The statistical structure of the environment governs the actions we take. For example, the probability that the Toronto Transit Commision will not abide by its schedule is unfortunately high, and many Torontonians have optimized a strategy to deal with this. However, sometimes the relevant variables in the environment for inferring the probability of various outcomes are hidden. A partially observable Markov decision process (POMDP) is a formalism for studying decision making when the environment's states are partially hidden. A POMDP consists of a set of partially observable states in which an action can be taken, a set of action-dependent transition probabilities, and a set of probabilities for reinforcement in different states. We have developed a novel behavioural paradigm using a Y-maze to test the performance of mice on a POMDP task. We report that mice are able to learn and alter their behavioural strategies to reap greater rewards in a POMDP task over time. Using immediate early gene imaging, we examine whether these strategies are mediated by different neural substrates based on the delay between POMDP tasks, and the stability of the state transition probabilities. This work can inform

our understanding of the neural systems that mediate behaviour when environmental states are partially observable. It also has the potential to impact the development of artificial intelligence agents and provide further understanding of systems consolidation.

3-F -197 Interactions of Reading and Semantics Along the Ventral and Dorsal Visual Processing Streams

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Separable semantic sub-systems, such as those representing knowledge for action, colour, and shape, are processed in independent networks of the brain. For example, the semantic sub-system for action processing is more dorsal (occipital-parietal-frontal), while the sub-systems for visual semantics are more ventral (occipital-temporal-frontal). There are also corresponding streams of processing in reading: the ventral-lexical stream is preferentially activated during familiar exception word (e.g., yacht) reading, while the dorsal-sublexical stream is preferentially activated during phonological decoding (e.g., pseudohomophones, PH, such as yawt, which sound like real words). Semantic priming was used to examine the sharing of the action semantic sub-system with the dorsal-sublexical reading stream, and the visual semantic sub-system with the ventral-lexical reading stream. Participants read a word or PH after reading a prime that required imagining either performing an action word or visualizing an object word. Word targets preceded by visual primes produced faster naming reaction times (RT) than those preceded by action primes, but the size of priming effects did not differ. A second experiment degraded the target words to further examine whether priming is influenced by scaling effects on RT. The results suggest that the visual semantic sub-systems may be more readily accessible for word naming than the action semantic systems, given that the shared stream ventral activation of visual semantics and word reading may be more commonly used in English.

3-F -198 Cue-place memory representation and interaction in CA1 during spatial navigation and reorientation in rats.

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The CA1 region of the rat hippocampus encodes both cue and place aspects of memory. Previous reports on cue and place representation in CA1 have examined single-cell and population activity dynamics during passive exploration of an environment or when actions are directed to either cue or place features in memory tasks. To better understand cue and place memory representation in CA1, and how these features interact during goal-directed navigation, we investigated population activity during memory retrieval in CA1 in a novel water task with two visibly distinct platforms, using immediate early genes Arc and Homer1a as markers of neural activity. Our results demonstrate that, after training, relocation of platforms to novel locations in the pool induces global remapping of the memory code, that is reflected in altered navigation and rapid learning of new cue-place information. By contrast, after training, exchanging platform locations in the pool induces less remapping that is reflected in persistent navigation to previous goal locations. These findings add to a growing literature characterizing the nature of cue and place memory representation in the rat hippocampus, and make a novel contribution to understanding the nature of cue-place memory interactions and the behavioural relevance of population remapping of memory codes in CA1.

3-F -199 Feature cells remap place selectivity in virtually navigating primates

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The hippocampus is critical for spatial navigation and declarative memory. The mechanistic bases of these two different functions have been studied largely independently across species; whether and how non-spatial mnemonic features of the environment shape place selectivity of single neurons has been difficult to study due to limitations of behavioural monitoring and neurophysiological recording. To address these limitations, we recorded single-neuron activity from the hippocampi of two rhesus monkeys while they navigated through a custom virtual maze to complete two tasks: a foraging task and a context-object associative memory task. Here we report classical place cell activity amongst hippocampal neurons in virtually navigating monkeys while they complete both tasks. A machine learning algorithm accurately predicted the position of the animal in the virtual environment from the activity of these place cells. However individual place fields of most neurons, and the ensemble code for space dramatically changed between tasks. Ensemble spatial codes diverged primarily in areas of the maze that required context-object comparison and choice in the associative memory task. Further examining of trial feature selectivity in these regions of the maze revealed that many neurons dynamically encode task-specific non-spatial features (objects, contexts and their conjunction both prospectively and retrospectively). Therefore, the spatial codes of single neurons and neuronal ensembles flexibly remap between tasks to reflect behaviourally-relevant task features in cognitive space.

3-F -200 High dose running wheel exercise attenuates exercise-induced hippocampal neurogenesis in the rat

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Providing rodents with continuous access to a running wheel (RW) can increase hippocampal neurogenesis in the dentate gyrus. Since this RW paradigm results in excessive levels of exercise not typical of human exercise patterns or achievable in patient populations with existing co-morbidities and physical limitations (e.g. stroke survivors), we developed RW paradigms that more closely represent human exercise patterns (e.g. shorter duration, alternate days). Neurogenesis was measured in male Sprague-Dawley rats assigned to 4hr, 8hr, or 24hr RW access on alternating days (4A, 8A, or 24A), continuous daily RW access (24C), or sedentary conditions (SED). Running paradigms were continued for either 14 or 30 days. Proliferating cells were labelled with bromodeoxyuridine (BrdU; 50mg/kg/day, i.p.) during the first week of RW access. After 14 days, 24A rats had significantly more surviving BrdU positive cells in the dentate compared to SED, 4A, or 8A rats. In contrast, following 30 days of RW access, 4A and 8A rats had significantly more surviving BrdU positive cells compared to SED, 24A, or 24C rats. Further, linear regression analysis established a negative relationship between running distance and surviving BrdU positive cells in the 30-day cohort (R^2=0.40). These findings demonstrate that moderate levels of RW exercise are superior to higher levels at promoting hippocampal neurogenesis. These results suggest that populations that cannot achieve high levels of exercise may still benefit from regular exercise and that overtraining may attenuate exercise-induced neurogenesis.

3-F -201 EXAMINING SEX DIFFERENCES IN ANXIETY-RELATED BEHAVIOR AND HIPPOCAMPAL THETA ACTIVITY IN RATS

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Hippocampal theta is an oscillatory activity pattern (4-14 Hz) that has been linked to ?fear/anxiety? states in rodents. To date, very few studies have systematically compared anxiety-related defensive behavior and hippocampal theta activity in males and females. Thus, we examined exploratory behavior in the elevated plus maze, a commonly used assay of ?anxiety? in rodents, and male and female rats. Females exhibited higher amounts of open arm activity (number of open arm entries and duration) compared to males, indicative of reduced ?anxiety? in females. Subsequently, using in same animals under deep urethane anesthetisa, hippocampal theta (elicited by electrical stimulation of the brainstem reticular formation) was recorded in the CA1 subfield. In comparison to females, males showed a small trend towards higher theta frequencies during brainstem stimulation, as well as a stronger suppression of theta frequency when administered the anxiolytic compound buspirone (10 mg/kg, i.p.). Ongoing analyses examine the potential relation of theta frequency and ?anxiety-like? behavior in individual animals. A more complete description of sex differences in defensive behavior and related neural mechanisms are important to advance out understanding of the neurobiological basis of ?fear and anxiety? states in mammalian species (supported by NSERC).

3-F -202 Exploring the Aversive Properties of Impaired Glucose Metabolism in Laboratory Rats

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There is evidence that hypoglycemia alters mood state in humans and induces depressive-like behaviours in animals. Therefore, it is conceivable that impaired glucose metabolism induces an aversive state that promotes avoidance behaviour. To test this hypothesis, we used the glucose antimetabolite 2DG to produce conditioned place avoidance (CPA) in rats and examined whether pharmacological manipulation of monoamines alters this effect. In experiment 1, 0, 300 or 500 mg/kg 2DG SC was paired with an initially preferred compartment during conditioning; avoidance behaviour was measured by comparing time spent in this compartment before and after conditioning. Experiments 2 and 3 measured blood glucose and corticosterone under the same conditions to characterize the physiological effects of 2DG. In experiments 4 and 5, 0, 10, or 40 ug/kg clonidine or 0, 10, or 30 mg/kg bupropion was administered concurrently with 500 mg/kg 2DG to alter monoamine activity and hence alter CPA. Results demonstrated that rats spent less time in the 2DG paired compartment and that clonidine and bupropion attenuated this effect. Blood glucose concentration increased after 2DG administration and bupropion abolished locomotor deficits found during 2DG conditioning. These results suggest that 2DG is a glycemic stressor that can produce CPA. Thus, it is conceivable that glycemic stressors can induce an aversive state that is dependent on acute NE hyperactivity. This supports our hypothesis and indicates that impairment of glucose metabolism may play a role in the psychopathology of mood disorders.

3-F -203 Improving visual perception in blindness: Multisensory training and electrophysiological evaluation of blindsight

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Homonymous hemianopia (HH) is the most common cortical visual impairment leading to blindness in the contralateral hemifield. However, patients with HH can preserve the remarkable ability to unconsciously perceive visual stimuli presented in their blindfield, a phenomenon known as blindsight. Unfortunately, this captivating residual ability is still misunderstood and insufficiently exploited within rehabilitation strategies. Nonetheless, multisensory stimulations enable cross-modal integration, thus

increase the superior colliculus (SC) neural activity which is hypothesised to be accountable for blindsight abilities. We therefore trained hemianopic subjects during 10 days and evaluated their saccadic performances, pointing abilities and electrophysiological activity. We used the visual mismatch negativity (vMMN) in EEG to determine automatic detection of changes in the blindfield and attentional switch without visual awareness. After training, we observed a behavioural improvement in saccadic performances, detection and localization of an unseen visual stimulus presented alone. This was correlated with a greater posterior negativity at 200 ms (vMMN) and the appearance of a positive wave around 300ms (P300) illustrating enhancement in the perceptual and attentional system. In conclusion, our results demonstrate the importance of bottom-up compensation therapies for visual rehabilitation and the effectiveness of the vMMN as an objective electrophysiological measure in blindsight.

3-F -204 How is neural activity in PMd and PPC influenced by bottom-up and top-down information about the value of reach choices?

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Many studies have shown that neural activity in sensorimotor regions not only represents the action plans to be executed, but also reflects the outcome values of the potential actions. In our study, outcome value was simultaneously indicated by 2 independent visual features to investigate how different kinds of information influence value-based modulation of activity in sensorimotor regions. A monkey was trained in a center-out delayed reaching task in which he's presented with two target choices. The value of each target is indicated by 2 independent features: bottom-up (BU) cues based on luminance, and top-down (TD) cues based on a line orientation. Each cue has 3 levels of desirability scores, and the sum of the two scores determines the number of rewards given upon a successful reach to that target. We are recording from dorsal premotor cortex and area 5 of posterior parietal cortex, which have previously been shown to exhibit value-related neural modulation. Data to date show that 1) both regions contain cells whose firing rate increases within 200ms from target-onset, and 2) when the decision is made based on BU information, directionally-tuned cells show divergence in the firing rate that reflects the monkey's choice, which occurs earlier than when the decision is made based on TD information. Additional analyses examine value-based modulation when only a single target is presented, and during trials in which the values of both targets are equal, but the BU and TD cues are in conflict. Support: CIHR (MOP-102662), CFI, FRSQ

3-F -205 Susceptibility to chronic social defeat is related to decreased hippocampal extrasynaptic NMDA receptor function in the CA1 region

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N-methyl-D-aspartate receptors (NMDARs) have been implicated in the pathogenesis of depression. Indeed, NMDAR antagonists such as ketamine exhibit fast-acting antidepressant effects. NMDARs can be found inside and outside glutamate synapses. Although extrasynaptic NMDARs (exNMDAR) have been implicated in the computation of synaptic currents and in neuronal death, their contribution to depression-related behavior remains unknown. We used a chronic social defeat model to separate mice into 2 groups: susceptible (expressing social avoidance) or resilient animals (normal social behavior). Using electrophysiological techniques, we found that mice that were susceptible to chronic social defeat had lower hippocampal CA1 exNMDAR function than non-stressed control and stressed mice that were resilient to chronic social defeat. In addition, we found that ketamine, which is a fast-acting antidepressant, selectively inhibited synaptic NMDAR (sNMDAR) function and enhanced the ratio of

exNMDAR/sNMDAR function. However, memantine, which preferentially inhibited exNMDAR currents, enhanced mice susceptibility to chronic social defeat. Finally, N-acetylcysteine, a drug that facilitates extrasynaptic glutamate release from cystine-glutamate antiporters on astrocytes, reduced mice susceptibility to chronic social defeat. Our findings suggest that mice susceptibility to chronic social defeat is related to low hippocampal exNMDAR function.

3-F -206 Assessing audiovisual temporal processing using prepulse inhibition and brainstem electrophysiology

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Our brain constantly integrates information from our different senses. The timing of this multisensory information determines whether we perceive the stimuli as occurring synchronously or asynchronously, and thus our reaction to it. Like humans, when rats are presented with coincident auditory and visual stimuli, their response is more robust than to either stimulus alone, indicating the increased saliency of an audiovisual stimulus. While many paradigms assess cortical audiovisual processing, none is able to assess if lower level integration exists, which may be important for basic sensory processing deficits. To that end, we designed a behavioural paradigm utilizing the acoustic startle response (ASR) and its modulation by a prepulse stimulus to assess a rat's ability to integrate audiovisual stimuli. Given that prepulse inhibition (PPI) relies on the pedunculopontine tegmental nucleus (PPT), we performed extracellular electrophysiological recordings in the PPT, to better understand the lower level neural integration of audiovisual stimuli. Both acoustic and visual prepulses induced significant PPI, depending on prepulse intensity. Consistent with our predictions, the level of PPI is most enhanced when auditory and visual prepulses are presented synchronously. Furthermore, electrophysiological results revealed neurons in the PPT that are capable of integrating auditory and visual stimuli. Future studies will use this behavior in animal models of compromised cognitive function in order understand mechanisms underlying impaired audiovisual temporal integration.

3-F -207 Socially induced hyperalgesia in an inflammatory pain model

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The social modulation of pain is nuanced by factors such as state-dependent motivation, relationships and stress. Previous work suggests that social contact in rodents and humans results in a cascade of endogenous opioids that reduce sensitivity to acute pain stimuli. However, the social modulation of on-going inflammatory pain and its influence on socially rewarding interactions remains unknown. Here we sought to uncover the influence of social reunion on subsequent pain responding and social interactions. To test this, we injected CFA (Complete Freud's Adjuvant) or saline into the hind paw of adult C57 mice. Cagemate dyads were either both in pain (CFA-CFA), one in pain (CFA-SAL) or control (SAL-SAL) and were separated for 24 hours following injection. Dyads were then tested for mechanical pain sensitivity and then reunited with their cagemate for 1 hour. Following reunion, dyads were re-assessed for changes in mechanical pain. We find that conspecifics experiencing inflammatory pain demonstrate increased mechanical pain sensitivity following social reunion, 1 day and 1 week following injection. Furthermore, allogrooming and social approach behaviours between conspecifics in pain during reunion were significantly reduced when compared to saline controls. Our results indicate that while social isolation increases motivation to interact, this socially motivated response is blunted in dyads experiencing inflammatory pain. This data parallels human chronic pain studies wherein social reward is impaired and in which certain types of social interaction enhance pain perception.

3-F -208 Pavlovian alcohol-seeking in rats: testing relapse using context-conditioned reinstatement and spontaneous recovery

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Animal models of relapse are critical for understanding the psychological and neural bases of addiction. The objective of the present study was to develop two new models of relapse using a Pavlovian alcohol-seeking paradigm in rats - context-conditioned reinstatement and spontaneous recovery. Male, Long-Evans rats (Envigo, 220-240 gm on arrival) that were acclimated to 15% ethanol (EtOH) in the home-cage received 12 Pavlovian conditioning sessions in which a 20 s conditioned stimulus (CS; continuous white noise) was paired with 0.3 mL of EtOH, which was delivered into a fluid port for oral consumption (8 CS trials/session; 2.4 mL EtOH/session). Rats then received 8 extinction sessions in which the CS occurred without EtOH, followed by 1 session in which EtOH was delivered as during Pavlovian conditioning, but without the CS. A control group received water instead of EtOH. Subsequently, responding to the CS alone at test was reinstated in both groups. Rats then underwent 8 additional Pavlovian conditioning sessions, followed by 8 extinction sessions and a test for spontaneous recovery. At test the CS occurred without EtOH. Robust spontaneous recovery occurred in rats that received a 23-day delay between the end of extinction and test; however, spontaneous recovery was not observed in a control group that received the same delay between Pavlovian conditioning and extinction. Our results provide strong evidence of spontaneous recovery of Pavlovian alcohol-seeking behavior. Ongoing studies will examine the impact of additional EtOH or water exposure on reinstatement.

3-F -209 Anxiety- and depression-like behaviours and memory impairment associated with elevated oxidative stress

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Oxidative stress is a common feature associated with cognitive impairment, anxiety, and depression. We have developed an oxidative stress-based model of age-related cognitive impairment (the HNE mouse) based on the gene deletion of aldehyde dehydrogenase 2, an enzyme important in the detoxification of endogenous aldehydes such as 4-hydroxynonenal (HNE), a lipid peroxidation product formed during periods of oxidative stress. However, the non-cognitive behavioural features of HNE mice are not known. Accordingly, we characterized anxiety- and depression-like behaviours in these mice. Three cohorts at different time points (3, 7, and 11 months of age) were subjected to a battery of behavioural tests including an assessment of mobility and exploration (open field test), anxiety-related behaviour (light/dark box and elevated plus maze), and depression-related behaviour (forced swim test and tail suspension test). Male and female HNE mice were analyzed by sex and age, and exhibited anxiety-like behaviours that were first observed at 7 months of age compared to wild-type mice. No significance differences or clear trends in depression-like behaviours were observed. These data reveal previously unreported behavioural changes in the HNE model of oxidative stress-induced cognitive impairment. We are currently using the sucrose preference test after subjecting mice to a mild chronic unpredictable stress (CUS) protocol to determine if differences in susceptibility to developing depression-like behaviours and deficits in memory are present in these mice following CUS.

3-F -210 Roles of the prelimbic and infralimbic prefrontal cortex in operant responding to appetitive, aversive and conflicting cues

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The prelimbic (PL) prefrontal cortex has been associated with the expression of behaviour motivated by reward and fear-related cues, whereas the infralimbic (IL) cortex has been characterized as suppressing fear and reward responding after extinction. However, both the PL and IL may be involved in controlling reward-seeking behaviour under the influence of a discriminative stimulus. The current study aimed to elucidate the roles of the PL and IL in responding to discriminative appetitive, aversive and conflicting stimuli. Rats performed an operant task wherein discrete stimuli associated with either positively valenced (sucrose reward), negatively valenced (foot-shock), conflicting or neutral outcomes were presented. Prior to testing, animals were infused in the PL or IL with muscimol/baclofen or saline. The results indicate that under extinction, inhibition of the PL or IL caused responding that was diminished to the appetitive cue, increased to the aversive cue, and without change to the conflict cue. With outcomes present, inhibition of the PL resulted in responding that was decreased to the appetitive cue and increased to the aversive and conflict cues, whereas inhibition of the IL caused no significant change in responding. The results support a role for both the PL and IL in the evaluation and integration of discriminative cues representing positive and negative valence. However, there may be differences in the specific functions performed by these regions, given the differential effects based on whether responding occurred with outcomes present or under extinction.

3-F -211 Hippocampal Involvement in a Binary Choice Reward Task

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The hippocampus is well-known to be involved in spatial navigation and contextual memory. However, prominent theories suggest that hippocampal projections to the ventral striatum also regulate dopaminergic activity. This suggests that the hippocampus may also play an indirect role in motivation and reward-based decision-making. To investigate this possibility, adult rats were given either sham or complete hippocampal lesions and then tested on a reward-based binary decision task with D-amphetamine (AMPH) or saline on-board. In this task, animals initiated trials with a nosepoke in a central port, and then locomoted to either a left or right feeder well to potentially receive a sucrose water reward. We found that lesions had little effect on measures of motivation (number of trials, intertrial interval), task performance (percent correct choice), or reward sensitivity (win-stay and lose-shift responding). Animals were then given systemic AMPH or saline prior to the task. We have previously shown that AMPH decreases win sensitivity and increases goal tracking in our task, both of which are modulated by increased dopaminergic tone in ventral striatum. However, while animals with hippocampal lesions demonstrated motoric sensitivity to AMPH (increased number of trials, decreased response time), win sensitivity and goal tracking were not affected. These null effects compared to control animals suggest that the hippocampus does influence motivation and decision-making.

3-F -212 DELTA OPIOID SIGNALING PROMOTES RESILIENCE TO CHRONIC STRESS IN MICE UNDER THE REPEATED SOCIAL DEFEAT PARADIGM

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The adaptation to chronic stress is highly variable between individuals. Resilience to chronic stress is a complex process recruiting several neurotransmitter systems. We hypothesized that enkephalin (ENK) signaling onto delta opioid receptors (DOPr) is specifically involved in the stress resilience. The aim was

to identify and characterize the functional contribution of ENK and DOPr in the development of stress resilience. The model of repeated social defeat allows to study stress resilience by mimicking the unpredictable social disruptions of daily life. For 10 consecutive days, the experimental mouse is placed in the vivarium of an "aggressor" (5 min/day) then the phenotype of resilience or vulnerability is evaluated using a social interaction test, based on the mouse?s aptness to interact with a novel aggressor. The mRNA levels of ENK, DOPr and brain-derived-neurotrophic-factor (BDNF), induced by DOPr signaling, were quantified in different brain areas by in situ hybridization. The mRNA levels of ENK are increased in the basolateral amygdala (BLA) and those of DOPr and BDNF in the hippocampus CA1 of resilient mice compared to vulnerable ones. In a group, mice were daily treated with a DOPr agonist, SNC80, throughout the social defeat paradigm. Administration of SNC80 induces a resilient phenotype in a majority of mice. Analyses of neuronal and synaptic plasticity by electron microscopy are underway. These results suggest that a dialogue between the BLA and CA1 acting through ENK transmission (via DOPr and BDNF) contributes to the development of stress resilience.

3-F -213 Probing pathway specific control of reward-seeking behaviour with in vivo optogenetic inductions of synaptic plasticity

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The use of in vivo optogenetic protocols to induce neural plasticity in the rodent brain is becoming increasingly prevalent, with an emphasis on their potential use in counteracting drug-evoked and other forms of plasticity in the nucleus accumbens (NAc). This integrative forebrain structure regulates reward-seeking behaviour, and its excitatory inputs likely encode motivational states and the presence of reward-associated stimuli. It is presently unclear, however, what specific information is encoded in each excitatory input to the NAc, and how the overall strength of these pathways influences decision-making processes. Here, we characterize how in vivo inductions of neural plasticity targeted to amygdala and midline thalamic projections to the NAc influence cued reward-seeking and self-stimulation behaviour. In vivo plasticity protocols that target these projections bidirectionally modulate the rate at which mice self-stimulate these pathways. This work demonstrates the effectiveness of in vivo plasticity protocols as a tool for studying pathway specific circuit function and reward-seeking behaviour.

3-F -214 Studying the Effect of Heartfulness Meditation on Brain Activity

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Long term meditation practice is increasingly recognized for its health benefits. Heartfulness meditation represents a quickly growing set of practices that is largely unstudied. Heartfulness is unique in that it is a meditation practice that focuses on the Heart. It helps individuals to connect to themselves and find inner peace. In order to deepen ones' meditation, the element of Yogic Energy ('pranahuti') is used as an aid during meditation. The purpose of this study was to determine whether consistent EEG effects of Heartfulness meditation be observed in sixty experienced Heartfulness meditators, each of whom attended 6 testing sessions. In each session, participants performed three conditions: a set of cognitive tasks, Heartfulness guided relaxation, and Heartfulness Meditation. Participants during the cognitive portion were required to answer questions that tested their logical thinking (CognitiveReflectiveTest) and creative thinking skills. (RandomAssociativeTest) The order of condition was randomly counter balanced across six sessions. It was hypothesized that Heartfulness meditation would bring increased alpha (8-12Hz) brain activity during meditation and better cognitive task scores in sessions where the

tasks followed meditation. Heartfulness meditation produces a significant decrease in brain activity (as indexed by higher levels of alpha and delta) during the early stages of meditation. This lead to the conclusion that Heartfulness Meditation produces a state that is clearly distinguishable from effortful problem solving.

3-F -215 Neuroanatomical Correlates of Home Cage Mouse Social Behaviour

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Social behaviour is an important function of the brains of humans and mice. However, the neurological basis of natural and longitudinal social interactions are poorly known. While mouse studies have been useful in understanding this relationship, social behaviour is typically quantified in artificial paradigms over short time scales. Using a combination of video and Radio Frequency ID (RFID) tracking, we tracked and phenotyped several groups of individually-identifiable mice in standard laboratory housing. RFID data was analysed using models from statistical physics and information theory to calculate social and non-social behaviour metrics. Fast semi-automatic quantification of video data was used for validation. Our behavioural measures captured known sociability differences in the BTBR and C57BL6/J mouse strains. BTBR mice were on average further apart from their cage mates than C57BL6/J mice. Furthermore, BTBR position probability was tightly locked to circadian rhythm; unlike C57BL6/J mice, whose position probability was highly influenced by their home group's configuration. C57BL6/J mice were monitored simultaneously over several weeks, through the development periods of puberty and early adulthood. In conjunction, Manganese-Enhanced MRI was used to obtain longitudinal in-vivo neuroanatomy over this observation period. By obtaining both neuroanatomical data and home cage behaviours in a high-throughput fashion, we were able to identify neuroanatomical structures that correlate with social behaviours and home cage activity.

3-F -216 Pre-existing difference in D1-MSN activity associates with susceptibility to depression-like behaviour

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Muir, J.1, Davidson, T.J. 2, Ramakrishnan, C.2, Deisseroth, K. 2, Nestler, E.J.3, Calipari, E.S.3, Bagot, R.C.1 1. Department of Psychology, McGill University, Montreal, QC, Canada 2. Department of Bioengineering, Stanford University, CA, USA 3. Icahn School of Medicine at Mount Sinai, New York, NY, USA Alterations in nucleus accumbens (NAc) activity have been linked to the pathophysiology of depression. Mice that exhibit depressive-like symptoms after chronic social defeat stress (CSDS) show distinct changes in NAc activity. However, the pre-existing individual differences that make certain mice resilient and others susceptible to stress are yet to be described. We hypothesized that individual differences in NAc activity present before exposure to stress may associate with future stress susceptibility. Using fiber photometry, we recorded activity in NAc D1- and D2- medium spiny neurons (MSN) in awake behaving mice. We report that, prior to stress, mice that later become resilient have higher D1 - MSN activity than mice that later become susceptible, an effect observed both in baseline neuronal activity and during social interaction. We suggest that reduced D1-MSN activity before defeat may be a predisposing factor for stress susceptibility. We also observed differences in D2- MSN activity temporally correlated with behavior, pointing to an additional role for D2-MSN in susceptibility to stress. These findings suggest a possible underlying mechanism of stress-induced susceptibility and offer the potential to predict at-risk individuals prior to encountering stress.

3-F -217 Single-trial measures of shared variability in area MT predict behavioral performance independent of firing rate

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The response of individual cortical neurons is highly variable. In contrast, decision-making in simple perceptual discrimination tasks (such as detecting a motion pulse in a visual scene) reflects population activity, and not the response of a single neuron. Population coding is thought to be enhanced by increasing firing rates and reducing shared variability in firing rates. Thus, we examined the impact of shared variability within populations of sensory neurons on decision-making in a perceptual discrimination task. To achieve our aims we developed a single trial measure of similarity between spike trains, and examined the extent to which they predicted the animal's behaviour. We report a predictive association between our similarity scores prior to stimulus onset, and behavioural outcomes in a motion detection task. Our findings deviate from previously reported results in that they capture fast fluctuations in neuronal activity that can be measured on each trial. These single-trial measures of shared variability were found to be as predictive of the animal's performance, as conventional firing rate measures. However, while firing rates were positively associated with behavioural outcomes, the presence of shared variability had a detrimental effect on behaviour. Furthermore, we demonstrate that firing rates and shared variability made independent contributions to behavioural outcomes. We show that a decoder that makes use of both features (firing rates and shared variability) captures our results better than one which uses only one of these features.

3-F -218 Role of physical contact during prior social interaction for social modulation of pain in a mouse model of Autism Spectrum Disorder

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The experience of pain in humans can be modulated by social interaction, social bonding, and empathy between two individuals. Gentle, socially-relevant touch can facilitate and maintain social bonding, and may therefore play a key role in the social modulation of pain (SMP). However, the effects of gentle touch are not fixed: individuals with Autism Spectrum Disorder (ASD) have reduced responsiveness to gentle touch that may contribute to decreased sociability and SMP. The study of gentle touch has been hampered by a lack of models to investigate physical, social contact between mice. The recent development of the Tube Co-Occupancy Test (TCOT), which measures the duration of time that mice physically co-occupy a shelter in an aversive environment, provides a novel means of quantifying social interaction between two stranger mice. We examine how prior social engagement in TCOT determines SMP in a mouse model of ASD. Using the valproate ASD model in CD1 mice, we first establish social engagement with TCOT and then measure SMP in mice dyads in the acetic acid assay. We predict that TCOT scores of control mice will correlate with reduced social modulation of pain in acetic acid assay, and that this correlation will not persist in ASD mice. Further work will directly vary the extent of physical contact in ASD and control dyads using TCOT to examine how physical interaction contributes to social bonding and SMP. This work will elucidate the relationship between physical contact and social bonding, and how misprocessing of social touch may contribute to social deficits in ASD.

3-F -219 Defining the Nature of Emotional Conflict Task Performance in Individuals with Major Depressive Disorder and Healthy Controls

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Etkin et al., (2006) introduced an Emotional Conflict Task demonstrating slower reaction time (RT) and reduced accuracy in healthy participants processing stimuli on trials with incongruence between task-relevant and task-irrelevant stimulus attributes (Conflict Generation/Stroop effect - cI trial), compared to trials with congruent stimulus attributes. This RT slowing was partially resolved when incongruent trials were preceded by an incongruent trial (Conflict Resolution - iI trial). Patients with major depressive disorder (MDD) are biased in processing emotional information. We hypothesized that Conflict Generation/Resolution may be greater in persons with MDD, and improve with favourable medication response. Data from 60 unmedicated MDD and 41 controls subjects who performed an Emotional Conflict Task was examined. MDD subjects were tested at baseline and 8 weeks after starting antidepressant therapy. Controls were tested at similar intervals. Two repeated-measures analysis of variance of group (MDD, control) x Time (Baseline, Week 8) x Task (Accuracy: congruent, incongruent)/(RT: congruent, incongruent) showed a robust Stroop effect across time in RT and accuracy within groups. No between group effects were observed. A multiple comparison corrected paired t-test indicated that Emotional Conflict Resolution (changes across cI and iI trials) was only demonstrated in control group accuracy at Week 8. While MDD and control groups demonstrated a Stroop effect, the Emotional Conflict Task was not helpful in differentiating between healthy control and MDD participants.

3-F -220 Investigating the functional and mechanistic impact of H2A.Z in associative learning and memory formation

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Epigenetic mechanisms such as histone variant exchange have emerged as crucial regulators of neural plasticity and particularly of learning and memory, though its function in the brain was only recently discovered by our lab. We showed that H2A.Z, a variant of histone H2A, undergoes active exchange on memory-related genes in response to learning and that virally-mediated H2A.Z depletion enhances memory in mice, suggesting that H2A.Z is a memory repressor. H2A.Z is also encoded by 2 genes that produce distinct protein products, H2A.Z-1 (encoded by the H2afz gene) and H2A.Z-2 (encoded by the H2afv gene). The distinct contribution of proteins encoded by the two genes in memory is not known. To isolate the contribution of the two H2A.Z genes, we created lines containing floxed genes for both H2afz/H2A.Z-1 and H2afv/H2A.Z-2, which our lab has crossed with mice expressing CreERT2 driven by the CamKIIa promoter, resulting in 3 new mouse lines: H2A.Z-1 knockout alone, H2A.Z-2 knockout alone, and dual knockout of both genes. Importantly, crossing mice with CreERT2 will produce mice in which Knockout of the target gene(s) were selectively induced in excitatory neurons in a temporally-controlled manner by an injection of tamoxifen. Mice were then exposed to contextual fear conditioning and tested 24 hr later in the same context with no shock. Preliminary findings have shown a role of H2A.Z-1 in memory, specifically that deletion of this gene leads to less freezing behaviour 24 hr after exposure to contextual fear conditioning.

3-F -221 Role of Prior Knowledge on Neocortical Learning: A Bayesian Perspective

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How is knowledge developed? One critical way in childhood is through a process called Fast Mapping (FM), wherein new words and concepts are inferred by exclusion, leading to rapid memory formation after as brief as a single exposure. Against canonical memory systems frameworks, FM learning can occur independently of the medial temporal lobe, instead implicating anterior and lateral temporal cortices crucial in semantic conceptual knowledge. To elucidate whether this learning occurs via statistical regularity extraction typical of neocortical learning or by conceptual integration, we developed a Bayesian Observers model of learning for an incidental encoding FM task in conjunction with magnetoencephalography. Using a preliminary norming study accounting for participant?s pre-experimental general knowledge of the world (reflecting the likelihood) and their accuracy in the FM task (reflecting the posterior distribution), we inferred each participants? prior distribution at 12 time-points, allowing us to identify changes in encoding behaviour. As hypothesized, individual differences in both learning capacity and next-day memory was reflected by more efficient application of prior knowledge during the task, indicated through increased correlation between the inferred prior distribution and accuracy. Preliminary data on how the inferred prior is associated with neuromagnetic activity in neocortical regions, and how this association changes as information is acquired, will be shown.

G - Novel Methods and Technology Development

3-G -223 TSPO ligand as a promotive agent in neuroprotection and neuroregeneration after severe cervical spinal nerve injury in rats

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Objective Etifoxine, as a compound of ligand of translocator protein 18kDa (TSPO), was induced to investigate the neuroprotective and regenerative effects on a severe cervical spinal nerve injury model, while progesterone was used for positive control. Methods 48 adult Fisher 344 male rats were used in this study. A right cervical spinal nerve crush injury (C5-C7) was performed to dysfunction the forelimb. Rats were randomly divided into 4 groups (n=12) based on different treatments: sham, vehicle of etifoxine, etifoxine and progesterone. 2-week (short-term) and 10-week (long-term) follow-up periods were designed to evaluate the neuroprotection and neuroregeneration. Histological examinations were performed at 2w postoperatively, while behavioral and electrophysiological evaluations were additionally taken at the end of 10w follow-up period. Results Etifoxine showed in short-term a significant neuroprotective effect when compared to vehicle group ($P<0.001$) and a similar effect to progesterone. In long term evaluation, limited promotive effects of etifoxine were found in sensory functional tests ($P>0.05$), whereas progesterone behaved more significantly. Both etifoxine and progesterone presented the beneficial effects demonstrated by a marked increase of amplitude and area under the curve (AUC) in evoked potential examinations($P<0.01$). Conclusions Etifoxine provided the neuroprotection and promoted axonal regeneration after a severe spinal nerve injury. However, the benefits were limited in sensory function recovery when compared with progesterone.

3-G -224 Transcriptomic profiling of hippocampal VIP-GABAergic neurons using patch-sequencing technique

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Basket cells (BCs) and long-range projection cells (LRPs) comprise the two vasoactive intestinal polypeptide (VIP)-expressing GABAergic subpopulations that can be found in the stratum oriens/alveus of the hippocampal CA1 region. To gain insights into the cell-specific molecules that could be expressed by these cell types we investigated their gene expression by using a single-cell patch RNA-sequencing approach in combination with post-hoc reconstruction in VIP-eGFP mice. After obtaining the whole-cell patch-clamp configuration cells were filled with biocytin and their cytoplasm gently aspirated for transcriptome analysis. We found that VIP-BCs and VIP-LRPs expressed a prominent set of 137 and 245 genes, respectively; many of them involved in cell metabolism and transcription regulation. Our analysis suggests two genetically distinct cell types within the same VIP-expressing population and reveals several highly expressed genes that may be used to discriminate them.

3-G -225 Instantaneous Tracking and Quantification of Local Protein Synthesis In Vivo

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Detecting when and how much a protein molecule is synthesized is important for understanding cell function, but current methods have poor cellular or temporal resolution or are destructive to cells. Here, we developed a technique to detect and quantify subcellular protein synthesis events at millisecond resolution in vivo. This Protein Translation Reporting (PTR) technique uses a genetic tag that produces a stoichiometric ratio of a small peptide portion of a split green fluorescent protein and the protein of interest during protein synthesis. We show that the split fluorescent protein peptide can generate fluorescence within milliseconds upon binding the larger portion of the fluorescent protein, and that the fluorescence intensity is directly proportional to the number of molecules of the protein of interest synthesized. Using PTR, we directly observed and quantified protein synthesis events at ribosomes in single cells over time in vivo. We use split red fluorescent protein to detect multiple genes or alleles in single cells simultaneously. We also split a photoswitchable fluorescent protein to photoconvert the reconstituted fluorescent protein to a different channel and arbitrarily reset the time of detection of synthesis events, continually over time.

3-G -226 Simple platform for chronic imaging of hippocampal activity during spontaneous behaviour in an awake mouse

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Chronic electrophysiological recordings of neuronal activity combined with two-photon Ca2+ imaging give access to high resolution and cellular specificity. In addition, awake drug-free experimentation is required for investigating the physiological mechanisms that operate in the brain. Here, we developed a simple head fixation platform, which allows simultaneous chronic imaging and electrophysiological recordings to be obtained from the hippocampus of awake mice. We performed quantitative analyses of spontaneous animal behaviour, the associated network states and the cellular activities in the dorsal hippocampus as well as estimated the brain stability limits to image dendritic processes and individual axonal boutons. Ca2+ imaging recordings revealed a relatively stereotyped hippocampal activity despite a high inter-animal and inter-day variability in the mouse behavior. In addition to quiet state and locomotion behavioural patterns, the platform allowed the reliable detection of walking steps and fine speed variations. The brain motion during locomotion was limited to ~1.8 µm, thus allowing for imaging

of small sub-cellular structures to be performed in parallel with recordings of network and behavioural states. This simple device extends the drug-free experimentation in vivo, enabling high-stability optophysiological experiments with single-bouton resolution in the mouse awake brain.

3-G -227 Detecting and characterizing repetitive movements in children with ASD.

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Autism Spectrum Disorder (ASD) affects approximately 1 in 68 children in North America, with the lifetime societal cost estimated at greater than $3 million per person. According to the Diagnostic and Statistical Manual of Mental Disorders, one essential diagnostic feature of ASD is the presence of restricted, repetitive, and stereotyped patterns of behaviors, activities, and interests (American Psychiatric Association, 2000). Stereotypies are usually documented during the interview using clinical, subjective scales. This makes difficult to detect changes in repetitive behaviors over time that may be important to evaluate the efficiency of behavioral therapy and/or pharmacological treatment. Our goal is to create a method to objectively quantify and characterize stereotypical behavior in a broad range of daily life activities. We manufactured a device to record arm/hand angular velocity and linear acceleration in three dimensions at high frequency and over a long time period. An algorithm was developed to find the stereotypies within the time series recorded and a gradient boosted trees algorithm was used to predict hand waving and hand flapping in test data. Our results show that it is possible to identify stereotypical movements associated with ASD among other natural behavior with an extremely high degree of accuracy (96%2). This quantitative approach to characterize repetitive behaviors longitudinally can be used in conjunction with classical clinical measurements to aid diagnosis, assessment and follow-up.

3-G -228 Development of a new algorithm for automated neuroanatomic segmentation in the adult mouse brain

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Post-mortem analysis of histological preparation of mouse brain sections is a essential method for fundamental and pre-clinical research in neuroscience. The availability of whole slide scanner systems offer the possibility to image quickly large brain sections, generating a large amount of data. Unfortunately, for now, the neurosegmentation of each region must be done manually on each brain section, making the work laborious and time consuming. We therefore decided to develop an algorithm allowing to detect the neuronal structures present on each of the digitized sections. For this purpose, we used the "Allen Mouse Brain Atlas" grouping together 132 coronal sections separated by 100 µm and annotated to a library of more than 700 referenced structures. After a huge work to validate the position of each structure, images were placed one behind the others to create a 3D matrix corresponding to a mouse brain. Subsequently, we created at first a reference brain by labelling cell nuclei (DAPI staining) and then a 5-level binarized reference brain in order to test the alignment between the reference matrix and the experimental images. Using this approach, neuroanatomic atlas contours can be projected onto the experimental brain section. Since biological sections are very thin and can be deformed, we have transformed/warped the atlas to allow the experimental and atlas data to be aligned optimally. Using an image quality control pre-sorting, our algorithm has a 90% accuracy. We anticipate that the analysis of large datasets will allow to optimize further the algorithm parameters.

3-G -229 Nanocontact printing of netrin-1 to study cellular haptotaxis and navigation

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Neuronal development is directed by multiple guidance cues to ensure correct wiring and innervation. A gradient of netrin-1 guides spinal commissural neurons to the ventral midline of the embryonic neural tube. In vitro studies of surface-bound netrin-1 mediated axon steering and turning are limited by the ability to rapidly, reproducibly and affordably generate protein density gradients. To address this challenge, our lab developed a set of digital nanodot gradients (DNGs) and a lift-off nanocontact printing technique to reliably print gradients of netrin-1 onto a glass substrate. The designed DNGs are monotonic and non-monotonic gradients made of discrete randomly or orderly distributed 200 nm^2 nanodots with increasing density. To facilitate appropriate cellular migratory responses to netrin-1 nanodots, the surrounding background, which we refer to as the reference surface (RS), must be adjusted to minimize its interference with the guidance cue. Our current RS is a mixture of two polymers; polylysine grafted to polyethylene glycol and poly-D-lysine, which we optimized by testing different polymer ratios and observing the haptotaxic migration of C2C12 cells on netrin-1 patterns. Our findings highlight the effect of the RS on cell-surface affinity and navigation. Additionally, our findings provide strong evidence that the RS must be optimized as a function of each guidance cue, the local density of nanodots, and the cells being studied. Next steps involve studying the response of different types of neurons to guidance cues patterned using the DNGs.

3-G -230 A Spinal Cord Phantom to Test and Standardize MEGA-PRESS gamma-aminobutyric acid (GABA) Measurements

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γ-aminobutyric acid (GABA) is the most prevalent inhibitory brain neurotransmitter and plays a significant role in neuroplasticity. However, due to low concentration and spectral peak overlap GABA is challenging to measure in vivo. The goal of this magnetic resonance spectroscopy (MRS) study was to assess whether measurement of an already challenging metabolite could be done in the cervical spinal cord, in vivo. This is important as the cervical spine can reveal information on the upper limb and its neuroplasticity. However, the spinal cord is in a difficult location due to bone associated B0 field inhomogeneity and magnetic susceptibility artifacts. In this study, a MEGA-PRESS MRS sequence, with a scan time of 11 minutes, was repeatedly tested on a home-designed and built spinal cord phantom that implemented a series of thin pipes, embedded in fluid, each matching the transverse dimensions of a human spinal cord. The concentration of GABA in each pipe was within healthy physiological range (1 and 2mM) and other dominant neurological metabolites were included (NAA, Cr, Cho, etc.) to test for the effect of spectral overlap with other resonances. Different voxel geometries were attempted, however the only reliable measurements were found using a $1cm^3$ cube-shaped voxel. Analysis using TARQUIN software provided repeatable and reliable GABA concentrations. Future work will involve in vivo spinal cord measurements in healthy subjects while including B0 and B1 correction schemes and integration of additional noise reduction techniques.

3-G -231 A critical assessment of functional methods to detect and quantify silent synapses

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Neuronal synapses exist in both active (AMPA-containing) and silent (AMPA-lacking) forms. Silent synapses are highly plastic and their relative abundance is believed to be a fundamental determinant of

the plasticity potential of neural networks. Due to sustained interest into their regulation, it is important to develop experimental approaches allowing fine-grained discriminability of silent synapse populations. Here, we considered the accuracy and robustness of several experimental methods for silent synapse detection, including single-synapse methods (two-photon glutamate uncaging, and electrical minimum stimulation) and a widely-used multi-synapse method (failure rate-based analysis, or FRA). We employed a set of experimentally constrained numerical simulations to directly compare the quantitative accuracy of these methods. We found that the multi-synapse FRA technique is characterized by low estimation accuracy and biologically implausible results, neither of which is attenuated by changes in experimental methodology. Additionally, a power analysis revealed that single-synapse methods required several orders of magnitude fewer samples than the multi-synapse FRA method for similar statistical power when discriminating mixed active and silent synaptic populations from active-only (null) populations. These results highlight the superiority of single-synapse binary classification methods in discriminating fine-grained changes in silent synapse populations, and provide a roadmap for future methodological advancements into silent synapse detection and quantification.

3-G -232 Comparing the Expression of Genes Related to Neurogenesis Process in C57BL/6J Mice Based on Data Available at the Allen Institute for Brain Science Website

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Background: Brain atlases are tools used to locate biological characteristics such as structures, connections, proteins or gene expression in different regions of the brain. These atlases have been disseminated to the point where tools have been created to store, manage and share the information they contain. Objective: This study used the data published by the Allen Institute for Brain Science website for mice (C57BL/6J) to compare the expression of neurogenesis-process related genes. Method and process: Genes of interest were searched for manually in each case (in situ hybridization for mice), energy expression were extracted and compute, and the results were graphed and analyzed under three methods (cluster analysis, principal components analysis and coexpression network). Results: Despite the differences in methodology, quantification process and algorithms used in the process, a low degree of similarity was found between expression data and typically neurogenesis area. We compare expression in a way that allows methods to infer and validate knowledge about different topics of comparing, for example, expression genes of stem cell or genes that controlled S phase in cell cycle. Conclusion: This type of study allows part of the relationship between structures and functions to be identified, by examining expression patterns and comparing levels of expression in different areas and anatomical correlations. The study concludes by discussing the importance of knowing, managing and disseminating comprehensive, open-access studies in neuroscience and importance of big data.

3-G -233 Development of a multi-colour optogenetic toolkit for studying cAMP and cGMP in living neurons

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Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are major intracellular signaling molecules that have interactive roles in a variety of physiological functions. However in neurons, the precise details of their spatiotemporal interactions are not fully known. To then study the interactive role of cAMP and cGMP, we established a dual colour optogenetic strategy to selectively activate cAMP/cGMP signaling in living neurons using different colours of light. We previously

used a blue light photoactivatable adenylyl cyclase (PAC) and its mutant (BlgC), which synthesize cAMP and cGMP, respectively, to study their postsynaptic signaling functions. To separately manipulate cAMP/cGMP levels in the same neurons, we optimized/prepared green and far-red light-sensitive adenylyl/guanylyl cyclases (AC/GCs) and examined them in combination by various light permutations in vitro. To manipulate light-sensitive enzymes at the single synapse level, we have used two-photon photoactivation in living hippocampal brain slices. We systematically characterized the two-photon properties of different light activated AC/GCs and established a dual two-photon photoactivation strategy in vitro. We found that longer wavelengths of two-photon light (>1,000 nm) efficiently activated the green and far-red light-sensitive enzymes, while shorter wavelengths (up to 1,000 nm) well-activated the blue light-sensitive enzymes. We will discuss in vivo applications of these optogenetic approaches for studying cAMP and cGMP signaling at both the synaptic and mouse behavioural levels.

3-G -234 Automated fine-scale three-dimensional paw tracking and posture classification system in mice

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Forelimb movements represent a refined feature of the mammalian motor system. Goal-directed limb movements integrate relevant sensory inputs and motor commands. The resulting movement trajectory and kinematics lie in a high dimensional space, which is intractable for manual rating. We developed an integrated hardware and software system that uses low-cost single-board computers, machine vision, and supervised learning to automate paw tracking and posture classification. Head-fixed mice were trained to pull a lever for a water reward upon hearing an auditory ¨go¨ cue while being recorded by a two-camera stereovision system. Previous implementations of machine vision for paw movement analysis only track the centroid of the paw, as the high deformability of the paw imposes a great challenge on automatically discriminating posture. To extract posture information from videos, we developed machine vision techniques to track a fluorescently dyed mouse paw from the videos, extract its geometric and kinematic features, and reconstruct the 3D movement trajectory during contact, grasping and release of the lever. We trained nonlinear classifiers (random forests and neural networks) using these features and 3D trajectories to estimate paw posture parameterized with openness, digit extent, and contact with the lever. In our study, we validated the robustness and precision of our system against a physical readout of lever position. Our approach allows for longitudinal automated assessment and comparison of fine-scale paw movements in health and disease.

H - History, Teaching, Public Awareness and Societal Impacts in Neuroscience

3-H -235 The Pedagogy of Vernacular Neuroscience across Higher Education Curriculum: Time to Bridge the Divide?

Andrea Valente[1]
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This poster proposes a pedagogy of vernacular neuroscience in general education courses by using life stories of individuals with neurological conditions (e.g. autism, epilepsy, cerebral palsy and stroke). It takes a case study approach by examining the pedagogical implications of the vernacularization of the neuroscience in 'neuro-autobiographies' of four women (Grandin, Hustvedt, Taylor and Martinez) who disclose their neuro disorders to a lay audience. This study is part of my dissertation which is grounded in complexity theory framework (Byrne & Callaghan), and rhetoric methodology (Gross) to analyse the

'neuro-autobiographies'. Today neuroscience attempts to reach out a broad lay public that falls outside its usual 'scientific niche'. Through various media platforms, neuroscience communicates to a diverse lay audience about its breakthroughs using a vernacular, everyday language. Ironically, the pedagogy of vernacular neuroscience seems to be absent from the higher education curriculum. The teaching and learning of neuroscience as a discipline housed in life sciences departments reinforces 'the two cultures divide' model (C.P Snow) isolating the hard-core sciences from the soft ones. As consequence, undergraduates of the two cultures miss a holistic education: Neither have the life science students the opportunity to explore the vernacularization of neuroscience in popular narratives, nor have the humanities students the chance to process neuroscientific information in a vernacular style with everyday examples. Hence, this study is an attempt to bridge the divide.

3-H -236 Inducing critical thought in the era of the fast and furious availability of information: A focus on Neurohealth students

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Students have many sources of information available to them, with this information being available very quickly; afterall, we are dealing with the "wired" generation. When teaching students about health and illness, it is important that they be able to be critical of all this information, particularly when not from scientific sources. The representation of various health conditions may be inaccurate; however, even accurate information may be presented in such a way as to influence perceptions and sustain stereotypes about certain health conditions. This is particularly true when disorders of mental health are presented in the media. In our advanced Neurohealth course, students perform an analysis of the media representation of a particular health condition. We first discuss various media to which they are exposed; these include print media (newspapers and books), films and television shows, online medical sources, blogs, and social media, to name a few. The students then choose a health condition with an underlying neurological pathophysiology. While they must first research the existing scientific literature to present the epidemiology, pathophysiology and psychosocial impact of their chosen neurohealth condition, they then choose a medium of interest and investigate the representation, using a content analysis approach, of their neurohealth condition in this medium. The goal of this approach is to help sensitize students to how these conditions are represented in the media to which they are exposed daily and help them become more critical of these representations.

3-H -237 BrainReach North - Mission Cerveau Nord

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BrainReach North is an education outreach program providing introductory neuroscience lessons to elementary and secondary school students in remote areas of Quebec, with a particular focus on indigenous communities. An extension of the highly successful Montreal-based BrainReach program, BrainReach North is run entirely by graduate student volunteers. The web-based program provides lesson guides for teachers to lead hands-on activities in their own classroom that guide students through basic brain science concepts. The goal of BrainReach North is to spark interest in science using topics children can relate to, such as the five senses, emotions, and memory, while emphasizing the scientific method and critical thinking skills. A focus on northern and remote communities helps ensure all students have access to enrichment opportunities. At the same time, graduate neuroscience student volunteers are given a chance to develop teaching and content development skills. BrainReach North is currently available in the Central Quebec and Cree School Boards, with the goal of expanding to schools

in the Kativik School Board in the coming year. BrainReach was the winner of the 2016 CAN Advocacy & Outreach Award for best student initiative promoting neuroscience to the public.

3-H -238 A History of Endocrine Disrupting Compounds and Their Role in Neurodevelopment

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The notion that chemicals in the environment may have long-lasting adverse consequences on both the developing fetus and during post-natal brain development has been well established. Indeed, the finding that the human placenta does not act as a complete barrier for the fetus, as was once thought, leant itself to the idea that exposing the mother to toxicants might also have an effect on the fetus. This, coupled with Behnsen's discovery in the late 1920s that the blood-brain barrier in humans is not fully developed until at least six months after birth, suggested that these toxicants could indeed have serious adverse neurodevelopmental consequences for the fetus. Moreover, while highly proficient, the blood brain barrier is not able to block the passage of all chemicals. In parallel, research examining central nervous system sexual differentiation sought to understand the role of hormones in early embryonic sexual dimorphism of the brain. The term endocrine disruptor was coined in 1991 to signify chemicals that disrupt endocrine systems; these have since been associated to many developmental disorders, including those involving sexual development, developmental delays and autism. Furthermore, endocrine disrupting compounds have the ability to interfere with normal hormonal function resulting in atypical sexual dimorphism in sensitive brain regions. A variety of endocrine disrupting compounds and discoveries of their differential influences on male and female neurodevelopment, as well as their potential contribution to neural disease and disorders, will be highlighted.

IBRO International Brain Research Organization

3-IBRO-239 Cerebrolysin remodels neuronal morphology in the limbic system and improving behavioral deficits in a rat model of autism

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Prenatal valproic acid (VPA) exposure has been proposed as an animal model reproducing both behavioral and anatomical impairments of autism spectrum disorders (ASD). Some of the behavioral features of the model are decreased number of social behavior, impairments in learning and memory and hyperresponsiveness to novel environment. Due to unknown etiology and the wide symptomatology, there is not a unique treatment for ASD. Almost ten years ago, took place some clinical trials using Cerebrolysin (CBL), which is a peptide preparation mimicking the action of neurotrophic factors; inyecting CBL to kids with autism they found positive results. However, there are not others human trials or animal models reports which confirm these results. For that reason, the aim in this work was evaluate the effect of CBL administration from postnatal day (PD) 5-21 on male pups (age 21PD), prepuberal (35 PD) and adult rats (70 PD) prenatally VPA-exposed. We assessed sociability (social interaction test), learning and memory (using novel object recognition test) and stress response (locomotor activity in a new environment); plus, neuronal morphology and density of dendritic spines were analyzed by Golgi-Cox stain in prefrontal cortex (layer III), dorsal and ventral hippocampus and basolateral amygdala. VPA rats showed low sociability, impairments in learning and memory and hyperresponsiveness to stress; additionally, abnormal neuronal morphology and connectivity were found. Most of these impairments were corrected by CBL, probably by its neurotrophic activity.

3-IBRO-240 Anti-seizure activity of Annona Senegalensis on the Genetic Epilepsy with Febrile Seizure Plus (GEFS+) model in Drosophila Melanogaster

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Objective: This study investigated the effect of Annona Senegalensis extract (AS) on seizure behavioral responses in GEFS+ using mutated K1270K and K1270T knock in flies to understand its mechanism of action. Methods: Wildtype (red) and mutant flies (K1270K and K1270T) were fed with only cornmeal food (Controls) or with food that contains 5.3mg/ml and 10.6mg/ml of aqueous leaf extract of AS (Treated) in groups of 10 -12 per vials. Flies were transferred into empty vials, acclimatized to the new environment for 5-15 min and observed in the vials following immersion into water bath at 40oC. The number paralyzed, seizing or standing were recorded at 5 seconds intervals for 2 minutes. Results: Control flies show an increased activity and approximately ~10 % of animals seize or become paralysed due to the heat. Number of standing animals in mutant flies decreased with time while the number of seizing and paralyzed increased reaching a dramatic ~25% of flies seizures and ~23% paralysed after 2 minutes. There was a significant difference between wildtype and mutant animals. AS treated groups showed a significant increase in percentage of flies standing reaching ~55% with 5.3mg/ml and further improving to ~82% with 10.6mg/ml. This improvement is due to a slight decrease of the percentage of flies seizing but mainly to a fantastic decrease of the number of flies paralysed ~3% with 10.6mg/ml. Conclusion: AS treated flies became less susceptible to seizure phenotypes compared with untreated group. AS interfere with seizure mechanism and possibly act by stabilizing channel activity.

3-IBRO-241 Chronic exposure to the anti-HIV Drug, nevirapine, impairs cognitive function, promotes oxidative stress, β-secretase 1 expression and increases β-amyloid plaques in mouse hippocampus

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Antiretroviral therapy has been shown to induce oxidative stress in HIV-infected individuals. Studies have demonstrated that an increase in reactive oxygen species due to lipid peroxidation stimulates β-site APP cleaving enzyme 1 (BACE1) expression and β-amyloid accumulation. Therefore, the aim is to investigate whether anti-HIV drugs, tenofovir and nevirapine, induce cognitive deficits and promote hippocampal BACE1 expression and β-amyloid accumulation in mice. Female Balb/c mice were orally administered single dose tenofovir (3.4mg/kg), nevirapine (3.0 mg/kg) or vehicle daily for 8 weeks. After 6 weeks, locomotor activity, spatial learning and memory and recognition memory were assessed. After chronic treatment, animals were sacrificed and the hippocampus isolated. 4-hydroxynonenal levels, BACE1 expression and β-amyloid plaques were measured. Our findings showed that chronic exposure to nevirapine impaired learning and memory and increased lipid peroxidation to a greater than tenofovir. Cognitive deficit caused by nevirapine was associated with an increase in BACE1 expression and β-amyloid plaques. In conclusion, chronic antiretroviral treatment induced oxidative stress. Nevirapine appeared to be more neurotoxic than tenofovir, increasing BACE1 expression and β-amyloid plaques, thus affecting learning and memory. These findings further support the hypothesis that antiretroviral drugs play a role in HIV-associated neurocognitive disorders. Keywords: HIV-associated neurocognitive disorders; antiretroviral therapy; Lipid peroxidation; BACE1; β-amyloid

3-IBRO-242 Oxidative damage impairs cholinergic function in cultured neurons exposed to Amyloid-beta oligomers

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The neurotransmitter acetylcholine is synthesized by the enzyme choline acetyltransferase (ChAT), which is also a marker of cholinergic neurons. Disturbances of cholinergic neurotransmission are implicated in several CNS pathologies, including Alzheimer's disease (AD), a prevalent form of dementia. Early work by our group, using chick retina as a CNS model, showed that ChAT activity can be specifically down-regulated by excitotoxic stimuli, before any changes in cell viability or enzyme levels occur. This effect was shown to depend on calcium influx and nitric oxide (NO) production. More recently, we observed similar results after treating cholinergic neurons with oligomeric forms of the amyloid-β peptide (AβOs), diffusible synaptic toxins found in AD brains, regarded as possible culprits of the disease. Notably, we showed that this effect was linked to excitotoxicity and to the production of reactive oxygen species (ROS). In the current work, we expand these observations to cultured neurons of the rat septal region and identify oxidative modifications involved in the loss of cholinergic activity. Using SNO-RAC and AMS labeling of thiols we show that cysteine modifications are apparently unrelated to ChAT inactivation. Tyrosine nitration, on the other hand, is shown by immunoassay to be induced in the enzyme by treatments with excitatory amino acids, AβOs or NO donors, and to correlate well with the loss of ChAT activity. These results suggest a novel mechanism for cholinergic dysfunction, which precedes neuronal death, and may be relevant in early-stage AD pathology.

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