The Canadian Association
for Neuroscience presents

10th Annual Canadian Neuroscience Meeting 2016

@10

MEETING PROGRAM

May 29–June 1, 2016

Toronto, Ontario
Sheraton Centre Toronto Hotel

CAN-ACN @10

CANADIAN ASSOCIATION FOR NEUROSCIENCE
ASSOCIATION CANADIENNE DES NEUROSCIENCES

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Sunday, May 29

Presidential Lecture

JOHN O'KEEFE, University College London

Hippocampus as a cognitive map: past, present, and future.

Sponsored by: *Hotchkiss Brain Institute*

Locating ourselves in familiar environments, navigating flexibly around those environments, and remembering where important objects can be found in them represent some of the most fundamental cognitive tasks that the brain performs.

In the first part of my talk, I will describe the discovery of the place cells and how they led to the formulation of the idea that the hippocampus was the neural substrate for a cognitive map.

In the second part I will summarise our current understanding of the components of the map: the place, direction, grid and boundary cells in the hippocampal formation. In addition to providing inputs for the construction of place representations, the grid cells appear to be good candidates to provide the distance metric for the map although recent evidence from our own lab suggests they may not be able to do this in all environments.

In the third part, I will look a little bit into the future and describe some of the emerging technologies which I think will give us a greater insight into how the networks of cells in the hippocampal formation cooperate together to provide spatial representations.

Monday, May 30

Plenary Symposium

Chair: **FRANCES SKINNER**, Krembil Research Institute/UHN and University of Toronto

Toward Theoretical and Experimental Synergies in Neuroscience

While it is abundantly clear that modeling and theory is needed in neuroscience, it is not always clear how to bring about synergies with experiment. I will briefly describe some of my older work along with recent work from my lab as examples of such synergy and its evolution.

MAURICE CHACRON, McGill University

Cracking the neural code

Understanding how neurons process sensory information in order to give rise to behavioral responses (i.e. the neural code) remains a central problem in neuroscience. Here I will highlight some of our recent advances towards understanding neural coding that have been successful because of a tight integration between experimental and theoretical approaches in both the electrosensory system of weakly electric fish and the vestibular system of macaque monkeys. These two sensory systems appear to be quite different at first glance: one senses electricity while the other senses movement. Despite these differences, I will show that the neural coding strategies used by both systems are not so different from one another when the statistics of the natural electrosensory and vestibular environments are actually

taken into account. I will then show how simple phenomenological models can explain these coding strategies and their importance in establishing a paradigm shift towards understanding neural coding in these two systems. These approaches are likely to shed new insights into developing general theories of neural coding applicable across systems and species.

GAUTAM AWATRAMANI, University of Victoria

The Fine Balancing Act of GABAergic/Cholinergic Retinal Starburst Amacrine Cells

Over the last 25 years, a surprisingly large number of neurons with the ability to co-release both fast excitatory and inhibitory transmitters have been identified throughout the brain. However, the computational benefits of dual transmitter release remain poorly understood. It is possible that inhibition and excitation arising from a common source leads to cancellation. Alternately, co-transmission of inhibitory/excitatory transmitters may allow neural networks to maintain balanced states, especially under limiting conditions where network variability is high. Here, I will address the role of co-release of ACh and GABA by starburst amacrine cells, which are integral components of the retinal direction-selective circuit. I will discuss how we have combined pharmacology, optogenetics and linear regression methods to estimate the spatiotemporal profiles of GABA, acetylcholine and glutamate signalling evoked by moving stimuli, and formulate a new theory on how the network of starbursts finely controls the balance of inhibition and excitation that shapes directional responses of downstream ganglion cells.

Featured Plenary Speaker

LARRY ABBOTT, Columbia University

Sense from Randomness in Neural Circuits

Many neural circuits are interconnected with remarkable precision, but others appear to be wired randomly. How extensive is randomness and how can randomly connected circuits perform useful functions? I will address these questions using experimental data and models from a number of different systems. I will also discuss how a characteristic feature of randomly wired neural populations, small numbers of synapses, optimizes their performance.

Tuesday, May 31

Plenary Symposium

Reward learning: neurons, circuits, and behavior

Chair: **JONATHAN BRITT**, McGill University

Reward seeking and reward consumption in relation to glutamate input to the nucleus accumbens

The decision to allocate effort in pursuit of reward is a function of the nucleus accumbens. Glutamate inputs here likely encode goals and action plans. To gain insight into these signals, we measured

pathway specific glutamate input activity in mice during a discriminative reward seeking task using GCaMP-based fiber photometry.

STEVE LAVIOLETTE, The University of Western Ontario

Hunting the Brain's Addiction Switch: Implications for Neurobiological and Clinical Approaches to Drug Dependence

The 'disease model' model of addiction has dominated the clinical and pre-clinical realms of drug abuse research for decades. This paradigm considers addiction primarily from the perspective of chronic and static alterations to brain reward circuits, leaving the brain in a permanently altered state of drug dependence and persistent vulnerability to relapse. However, considerable evidence demonstrates that the process of addiction involves discrete molecular and neuronal events occurring both in primary reward processing regions such as the ventral tegmental area, and in neural regions critical for reward-related associative memory formation, such as the amygdala and prefrontal cortex. Equally important, mounting evidence points to the remarkable plasticity of drug-related exposure effects on select brain reward and molecular memory mechanisms, as well as the reversibility of many of these drug-induced neuroadaptations. Using pre-clinical rodent models of opiate addiction, our research program has focused on identifying addiction switching mechanisms in the mammalian brain that control separate and distinct reward and associative memory pathways. We have found that both the primary rewarding effects and associative memories related to opiate exposure depend upon separate neuroanatomical, neuronal and molecular substrates. In turn, these addiction switching mechanisms are controlled by the brains opiate exposure state during either the acute, early rewarding effects of opiates vs. the motivational effects of opiates after dependence and withdrawal has developed. This presentation will discuss the implications of these addiction-related plasticity mechanisms in terms of re-conceptualizing our theoretical, neurobiological and clinical approaches to addiction treatment.

RICK BENINGER, Queen's University

Inverse incentive learning: decreased responding to stimuli associated with low dopaminergic neurotransmission

Incentive learning is the acquisition by neutral stimuli of an increased ability to elicit approach and other responses. Inverse incentive learning (IIL) is the loss by stimuli of ability to elicit approach and other responses. When dopamine neurons signal negative prediction error, IIL may take place. IIL is observed using (paired) rats treated with low dose haloperidol (e.g., 0.25 mg/kg) and tested once daily by placing them with their forepaws resting on a horizontal bar at a height of 10 cm. Paired rats descend immediately during the first session but over sessions latencies gradually increase. Control (unpaired) rats, tested following injection of saline but given haloperidol later in their home cage, continue to descend immediately over sessions. After 10 days, when both groups are tested following injection of haloperidol, increased descent latencies are observed only in the paired group even though both groups have a similar history of 10 haloperidol injections over 10 days. Results confirm the conditioned nature of the effect. The effect is seen with spiroperidol (0.25 mg/kg) or with bilateral microinjections of haloperidol (10 µg/0.5 µl/side) into the nucleus accumbnes but not dorsal striatum. Using c-Fos immunohistochemistry, lower neuronal counts were observed in the nucleus accumbens core and ventral pallidum of paired versus unpaired or saline control rats following testing all groups with haloperidol after 15 conditioning sessions. D1-like and D3 dopamine receptors have been differentially

implicated. IIL may take place when dopamine neuron firing is inhibited and may serve to reduce responsiveness to specific environmental stimuli.

Featured Plenary Speaker

ANN GRAYBIEL, McGovern Institute for Brain Research at MIT

The Striatum and Decision-Making Based on Value

This lecture will review experiments done in non-human primates and rodents suggesting that a circuit interconnecting the medial prefrontal cortex and striatum is differentially engaged in cost-benefit decision-making. This circuit leads through the striosomal system of the striatum toward the dopamine-containing substantia-nigra. This work is leading to the view that the striosome-matrix architecture of the striatum represents an evolutionarily ancient system that likely is associated in humans with emotional states including anxiety. We hope to contribute to an understanding of how these striosomal microcircuits are integrated into forebrain networks modulating movement and emotion.

Keynote Lecture

KARL DEISSEROTH, Stanford University

Integrated brainwide structural and functional analysis

Sponsored by: **Sick Kids Program in Neuroscience & Mental Health and The Center for Brain & Mental Health**

This talk will address the discovery and engineering of optical tools for precise, high-resolution investigation of intact biological systems, focusing on optogenetics (a technology for precisely controlling millisecond-scale activity patterns in specific cell types using microbial opsin genes and fiberoptic-based neural interfaces) and CLARITY (a technology for creating composites of biological molecules in tissue covalently linked to polymer hydrogels-- typically acrylamide-related-- allowing removal of unlinked tissue elements to create transparency and accessibility to macromolecular labels; the resulting new structure allows high-resolution optical access to structural and molecular detail within intact tissues without disassembly). The talk will focus on fundamental biochemical and structural discoveries regarding the operation of channelrhodopsins, strategies for targeting opsins and light to meet the constraints of the freely-behaving mammal, engineering of opsin genes spanning a range of optical and kinetic properties, development of high-speed behavioral and neural activity-readout tools compatible with real-time optogenetic control, recent advances in imaging of clarified tissue, and applications of these tools for circuit-based insight into motivated behaviors.

Wednesday, June 1

Plenary Symposium

Signal integration and plasticity

Chair: : **ROGER THOMPSON**, University of Calgary

Non-ionotropic functions of NMDA receptors

In the classical view, the NMDA receptor requires ligand binding (glutamate and glycine) in conjunction with membrane depolarization to open its ion channel and signal. I will discuss a new signalling modality where the NMDA receptor can activate downstream effectors upon ligand binding but without its ion channel activity.

KATALIN TOTH, Université Laval

Presynaptic calcium dynamics and information transfer at hippocampal mossy fibres

Presynaptic terminals play a key role in the translation of presynaptic firing patterns to a neurotramsitter release profile. Unique features of the presynaptic terminal will determine for example whether repeated firing leads to increased (facilitation) or decreased (depression) neurotransmsitter release. The process of signal translation is largely defined by presynaptic calcium dynamics. Neuronal calcium elevations are shaped by several key parameters, including the properties, density, and the spatial location of voltage-gated calcium channels (VGCCs). Short-term plasticity is synapse-specific, the same firing pattern is 'inetrpreted' differently by various neurons. What is the structural and functional reason of this diversity? How do the same building blocks endow terminals with synapse-specific features? We identified two distinct presynaptic mechanisms that are involved in short-term facilitation in hippocampal mossy fibers. The combination of multivesicular release and the recruitment of additional release sites act together to increase glutamate release during burst activity. This is supported by the compartmentalized spatial profile of calcium elevations in boutons and helps to expand the dynamic range of mossy fibers information transfer. We also identified the specialized roles different types of VGCCs play in neurotrmanitter release. N-type VGCCs permit fast glutamate release at a limited number of release sites and support short-term facilitation by enhancing multivesicular release through close association with active zones. In contrast, Ca2+ entry via P/Q-type VGCCs promotes the recruitment of additional release sites through activity-dependent homogenization of Ca2+ elevations. This is made possible by the strategic distribution of P/Q-type VGCCs further away from active zones. Altogether, our results highlight the specialized contribution of P/Q- and N-types VGCCs to neurotransmitter release.

KURT HAAS, University of British Columbia

In vivo imaging of brain circuit refinement

How neural circuits capable of complex information processing are formed remains a leading question in developmental neuroscience. Specifically, it remains unclear to what extent, and how, activity-dependent mechanisms interact with intrinsic genetic patterning. Functional circuit formation requires appropriate growth of each neuron's elaborate dendritic and axonal arbors and precise selection of hundreds to thousands of synaptic partners. We study these events using direct, rapid time-lapse imaging of neuronal growth, synaptogenesis and encoding in the awake developing brain, and post-imaging comprehensive quantification of large 4D datasets. We find that growth and connectivity of visual brain circuits arises through a program of experience-driven self-organization following rules that optimize encoding of the stimuli encountered. These rules act at the levels of growing dendritic processes and their synapses, but are influenced by tuning of neuronal firing. While shedding light on normal development, these mechanisms provide insight to the origins of neurodevelopmental disorders in which aberrant synaptic transmission drive abnormal growth and connectivity.

Plenary Speaker

NELSON SPRUSTON, Janelia Research Campus

Neuronal Diversity and Complexity in the Hippocampus

The hippocampus plays a crucial role in learning and memory. In rodents, this function is manifested in both spatial and emotional memories, which are thought to be encoded in the dorsal and ventral aspects of the hippocampus, respectively. Although the cellular organization of the hippocampus has been extensively studied using traditional anatomical methods, the diversity of cell types that comprise the circuit can now be probed with modern molecular, genetic, anatomical, and physiological approaches. My lecture will outline our progress toward using these techniques to explore the cellular organization and function of the hippocampus. We have identified subclasses of the major cell types in the hippocampus and we are relating the key molecular, anatomical, and functional features of these cell types, with the long-term goal of understanding how the menagerie of cell types works together to produce sophisticated functions such as spatial maps and memories. About half of the talk will feature new, unpublished data.

Symposium 1:

Voltage-gated ion-channels of the mammalian central nervous system

Chair: **Derek Bowie**, McGill University

Overview:

Voltage-gated ion-channels (VGICs) are a family of signaling proteins expressed throughout the developing and adult mammalian brain that are critical for its normal function but also implicated in many disorders, from pain sensation and epilepsy to dysfunction of immune cells. The symposium on "Voltage-gated ion-channels of the mammalian CNS" brings together 4 speakers whose work is at the forefront of this field of study. Dr. Lyanne Schlichter will discuss the role of VGICs in the activation of microglia, the resident immune cells of the brain. Dr. Terry Snutch will present his latest results on voltage-gated calcium channels in epilepsy and migraine. Bowie lab graduate student Ryan Alexander will present data on a new role for TTX-resistant sodium channel in the cerebellum. Finally, Dr. Ray Turner will describe how T-type calcium channels form complexes with specific potassium channels to effect multiple forms of control over cell excitability and signal processing.

Speakers:

Lyanne Schlichter, University of Toronto
Expression and regulation of K+ channels that control microglia functions

Microglia express an array of ion channels, including voltage-gated- (Kv1.3), Ca2+ activated- (KCa2.3, KCa3.1) and inward rectifier- (Kir2.1) K+ channels. Recent studies implicate each channel in discrete microglial functions from proliferation, migration, phagocytosis, and inflammatory mediator production. K+ channels help condition the brain's chemical milieu and regulate microglial interactions with neurons and glial cells. In non-excitable cells (e.g., microglia), K+ channels regulate the membrane potential and Ca2+ entry through store-operated Ca2+ channels, including CRAC. We have shown that CRAC, Kv1.3, KCa3.1 and Kir2.1 channels are highly expressed in microglia and can regulate migration, invasion, phagocytosis, and production of neurotoxic levels of reactive oxygen species. After CNS injury or disease, microglia acquire pro-inflammatory (M1) or anti-inflammatory (M2) activation states affecting cell function. However, little is known about the expression, regulation, and contributions of K+ and CRAC channels in different activation states. This talk will focus on the voltage-gated Kv1.3 channel with new findings on Kir2.1, KCa3.1 and CRAC channels in microglia.

Terry Snutch, University of British Columbia
New Insights into Familial Hemiplegic Migraine Type-1

Migraine is a common debilitating brain disorder characterized by severe headaches often accompanied with an aura involving sensory sensitivity and that has been linked to cortical spreading depression (CSD). Familial Hemiplegic Migraine type-1 (FHM-1) is an autosomal dominant disorder caused by missense mutations in the CACNA1A gene encoding the α1 subunit of voltage-gated CaV2.1 (P/Q-type) calcium channels. The talk will describe several aspects of the underlying pathophysiology of FHM-1 utilizing knock-in mice strains that reproduce many of the FHM-1 phenotypes described in patients. In part, these will include the contributions of CaV2.1 splice variation to spatial and temporal aspects of calcium channel dysfunction, and the analysis of CSD using both intrinsic optical signalling and a newly

developed in vivo diffusion-weighted MRI analysis methodology. The talk will also explore mechanisms by which pregabalin (Lyrica) may prove to be an effective anti-migraine agent through its effects on both pre- and post-synaptic signalling and CSD.

Ryan Alexander, McGill University
Regulation of voltage-gated ion channels by NMDA receptors in cerebellar stellate cells

The action potential (AP) is at the heart of the complex, oscillatory behavior of neuronal circuits regulated by a network of fast-spiking inhibitory interneurons. The AP has been shown to be made-up of a complex interplay of several voltage-gated ion channel families, including Na+ and K+ channels, which determine the threshold and frequency of firing rates. We have observed a long-term increase in cerebellar stellate cell excitability by signaling of NMDA receptors that modulates both Na+ and K+ channel activity. Local application of NMDA induced a persistent increase in spontaneous action current frequency during cell-attached electrophysiological recordings. During whole-cell current clamp recordings stellate cells exhibited a time-dependent increase in step-evoked AP frequency and hyperpolarization of spike threshold, both of which were eliminated by pharmacological block of CaMKII. Voltage clamp experiments revealed that CaMKII inhibition eliminates the development of a putative TTX-resistant Na+ current as well as a large outward K+ current. Our work provides insight into the role of NMDAR-dependent signaling in regulating inhibitory neuronal circuits of the cerebellum.

Ray Turner, University of Calgary
T-type calcium and potassium channel interactions

Neuronal excitability and signal processing relies on voltage- and Ca2+-gated ion channels. The view that ion channels operate independently of each other has been replaced with the realization that Ca2+-gated K+ channels can link at the molecular and functional levels in an isoform- and cell-specific manner to precisely control excitability and synaptic processing. We have uncovered several new interactions between T-type (Cav3 family) Ca2+ channels and both Ca2+- and voltage-gated K+ channels. This talk will highlight just two interactions between Cav3 and KCa3.1 (IKCa) or Kv4 K+ channels that enable distinct roles in cerebellum. In Purkinje cells, a Cav3 and IKCa channel association sets up a frequency-dependent filter to allow Purkinje cells to respond to sensory-relevant input. In stellate cells a Cav3-Kv4 complex creates a calcium sensing device to enable a new form of dynamic inhibitory regulation of Purkinje cells. With these findings the richness of Cav3 calcium interactions on cell excitability, synaptic processing, and circuit interactions become evident.

Symposium 2:

Structural and functional features of neural connectivity and plasticity in emerging and mature networks

Chair: **Jean-Claude Béïque**, University of Ottawa

Sponsored by: *Centre de recherche Institut universitaire en Santé mentale de Quebec*

Overview:

Specialized information processing in neural networks is critically dependent on the fine-scale organization of synaptic connectivity. This symposium will highlight recent advances on our understanding of how specific structural features of connectivity are acquired during key developmental periods and how they regulate processing properties in mature networks. Dr. Bamji will begin the session by presenting data on the molecular mechanisms underlying activity-mediated synapse formation and plasticity. Dr Lefebvre will then describe how neurons use a large family of recognition molecules to discriminate self from non-self for proper coverage of their dendritic territory. Dr. Béïque will follow and describe how developing dendrites encode spatiotemporal features of synaptic inputs and how these mechanisms spatially regulate synaptic connectivity. Dr. Araya will close the session by discussing how the structural plasticity of dendritic spines influences their electrical properties and how this ultimately regulates the transmission, integration and storage of information in mature neurons.

Speakers:

Shernaz Bamji, University of British Columbia
Regulation of synapse form and function through palmitoylation

Cell adhesion molecules are localized to sites of synaptic contact between nerve cells. Although, these molecules bridge pre- and postsynaptic specializations, they do far more than simply provide a mechanical link between cells. Indeed, synaptic adhesion proteins participate in the formation, function and plasticity of synaptic connections. Work in Dr Bamji's lab have demonstrated that the cadherin family of cell adhesion molecules plays a key role in regulating synapse plasticity, the cellular substrate for learning and memory. This presentation demonstrates that post-translational palmitoylation of cadherin-associated proteins is essential for activity-induced synapse plasticity, and demonstrates that that aberrantly increasing cadherin at the synaptic membrane can have deleterious effects on cognitive function including learning and memories associated with drugs of abuse.

Julie Lefebvre, University of Toronto
Molecular mechanisms of neuron self/non-self recognition in dendrite patterning and wiring specificity

Dendritic arbour patterns shape the ways in which neurons receive and integrate information. In some types of neurons, proper distribution of dendritic branches is achieved by a developmental process called dendrite self-avoidance, in which neurites from the same neuron repel each other. Self-avoidance establishes uniform and non-redundant coverage of a neuron's dendritic field, while allowing nearby neurons to overlap or form connections. We demonstrated that the large family of cell recognition molecules, the clustered Protocadherins (Pcdhs), mediates dendrite self-avoidance and self/non-self recognition in mammalian neurons. Deletion of the set of gamma-Pcdh proteins disrupts self-avoidance in retinal starburst cells, resulting in abnormal branch crossings, arbour morphology, and circuit functions. To determine the roles of Pcdhs in patterning brain circuits, we used CRISPR to generate mouse alleles that lack larger sets of Pcdhs, minimizing genetic redundancy. I will discuss our recent findings that establish critical roles for Pcdh cell-surface diversity in dendritic patterning, neuron survival, and live imaging studies revealing the cellular basis of dendrite-self-avoidance.

Jean-Claude Béïque, Université de Montréal
Spatiotemporal feature detection and plasticity rules in emerging neural networks

Neurons undergo robust dendritic growth and synapse formation during early postnatal development, marking a key period in neural circuit assembly. Despite the eminent role of calcium in synapse regulation, remarkably little is known about calcium dynamics during synapse development. Dr Beique will present results from whole-cell electrophysiology, two-photon calcium imaging and glutamate uncaging in hippocampal slices that outline a functional coupling between NMDA receptors and intracellular calcium release. This developmentally regulated calcium amplification mechanism was tuned to detect and bind spatially-clustered and temporally-correlated synaptic inputs, and enacted a local cooperative plasticity rule between coactive neighboring synapses. Consistent with the hypothesis that synapse maturation is spatially regulated, we observed clustering of synaptic weights in developing dendritic arbors. These NMDA receptor-dependent local plasticity rules are well positioned to instruct during postnatal development the assembly of synaptic microcircuit motifs that are suited for nonlinear dendritic integration, a fundamental feature of information processing at mature neurons.

Roberto Araya, University of Ottawa
Input transformation by dendritic spines of pyramidal neurons

In the mammalian brain, dendritic spines are the major recipient sites for excitatory synaptic information in the brain. Their peculiar morphology has inspired decades of theoretical and more recently experimental work in an attempt to understand how excitatory synaptic inputs are processed, stored and integrated in pyramidal neurons. Advances in electrophysiological, optical and genetic tools are now enabling us to unravel the biophysical and molecular mechanisms controlling spine function in health and disease. Here, Dr Araya will highlight relevant findings, challenges and hypotheses on spine function, with an emphasis on the electrical properties of spines and on how these affect synaptic transmission, storage capacity and integration of excitatory synaptic inputs. In an attempt to make sense of his data and that of others, Dr Araya propose that the raison d'être for dendritic spines lies in their ability to undergo activity dependent structural and molecular changes that can modify synaptic strength, and hence alter the gain of the linearly integrated sub-threshold depolarizations in pyramidal neuron dendrites before the generation of a dendritic spike.

Symposium 3:

Circadian regulation and clock genes link neuronal physiology to behavior

Chair: **Valerie Mongrain**, Université de Montréal

Overview:

Circadian rhythm research, especially that concerning the central nervous system, shapes understanding of the intimate relationship between circadian oscillators, comprising clock genes, and neuronal physiology and functions. As such, the molecular clockwork has been increasingly linked to neuronal and behavioral plasticity that has been previously recognized to be associated with various types of brain functions and behaviors including learning and sleep. The symposium will feature new data obtained from research in flies and rodents regarding both the regulation and the role of the circadian timing system and of its molecular elements and will highlight the important contribution of the Canadian research community to the state of the knowledge in circadian rhythm research. The last two

presentations of the symposium will also discuss the implication of these 'circadian' findings for social behavior and sleep regulation.

Speakers:

Valérie Mongrain, Université de Montréal
Clock genes, cell adhesion molecules and sleep regulation

Clock genes are governing a variety of cellular, metabolic and physiological functions in the mammalian brain. Clock genes have also been proposed to have both circadian and circadian-independent roles in regulating sleep. Our recent findings highlight that clock genes are regulating the transcription of cell adhesion molecules involved in synaptic formation, synaptic transmission and plasticity. More precisely, we identified two families of adhesion molecules, Neuroligin and Eph receptors, for which the expression is likely control by core clock transcription factors. Interestingly, we also found indications that these adhesion molecules are regulating sleep, which reveals a route by which molecular clock elements can regulate sleep.

Mary Cheng, University of Toronto Mississauga
G protein-coupled receptor kinase 2 (GRK2): putting the brakes on the circadian clock

G protein-coupled receptor kinases (GRKs) are a family of serine/threonine protein kinases that terminate G protein-coupled receptor (GPCR) signaling by phosphorylating the receptor and inducing internalization. In addition, some GRKs can phosphorylate non-GPCR substrates and regulate GPCR signaling in a kinase-independent manner. GPCRs are abundantly expressed in the suprachiasmatic nucleus (SCN), a structure in the mammalian brain that serves as the central circadian pacemaker. Various facets of circadian timekeeping are under the control of GPCR signaling, and thus are potential targets for GRK regulation. Despite this, little attention has been given to the role of GRKs in circadian rhythms. In this talk, I will discuss our latest findings regarding the functional involvement of GRK2 in mammalian circadian timekeeping in the SCN. Using grk2 knockout mice, we demonstrate that GRK2 is critical for maintaining proper clock speed and ensuring that the clock is well synchronized to environmental light cycles. Although grk2 deficiency alters the expression of key GPCR in the SCN, our study also reveals a more direct relationship between GRK2 and the molecular clock machinery.

Michael Verway, Concordia University
Dopaminergic modulation of rhythmic PER2 expression in the dorsal striatum

The clock protein, PER2 is involved in circadian modulation of dopamine neurotransmission in the dorsal striatum by effecting daily fluctuations in the levels of extracellular dopamine. I will present evidence pointing to a reciprocal connection between dopamine and PER2 expression, by showing that striatal dopamine depletion blunts the oscillations of PER2 in the dorsal striatum. The effect of dopamine on PER2 rhythms in the dorsal striatum is mediated by D2 dopamine receptors, as timed daily injections of the selective D2 receptor agonist quinpirole, but not injections of a selective D1 agonist can restore PER2 rhythms in the dopamine-depleted striatum. Findings of the existence of reciprocal relationships between dopamine and a core element of the circadian clock add a new level of complexity to the study of striatal plasticity and function in motor control, motivation, and reward processes and may offer a new way to understand the origin of circadian abnormalities characteristic of Parkinson's disease and drug addiction.

Joel Levine, University of Toronto Mississaugal
Circadian Control of Social Behaviour in Drosophila

Circadian clock circuitry in the brain regulates the timing of behavioural rhythms in Drosophila. Peripheral clock function in the oenocytes regulates the formation and expression of cuticular hydrocarbon pheromones that play a role in aspects of social interactions such as sexual recognition, courtship and mating. We have been investigating the signaling mechanisms that maintain synchrony between the brain clock and this peripheral oscillator. The basic phenomenon was published in Krupp et al. (2013) and we will extend the observations reported there in the symposium.

Symposium 4:

Low-level circuits for sophisticated sensorimotor control: lessons from four model systems

Chair: **J. Andrew Pruszynski**, Western University

Sponsored by: *Ontario Brain Institute*

Overview:

It is obvious that robustly integrating sensory inputs is essential for maintaining perceptual stability. It is less obvious, and thus often forgotten, that robustly integrating sensory inputs is also essential for generating accurate motor commands. Recently, substantial progress has been made in determining the neuronal mechanisms that underlie sensory integration for motor control. This symposium will highlight work by four new faculty - studying different sensory modalities, motor effectors and model systems - all showing the striking role of peripheral and subcortical circuits in sophisticated motor behaviour. Michael Hendricks will show how subcellular signalling contributes to sensory modulation during nematode orienting. Kathy Nagel will explain how synaptic and circuit mechanisms promote broadband transmission of olfactory stimuli and how they may contribute to drosophila navigation in a natural landscape. Tuan Bui will describe how a class of dorsal spinal interneurons enables cutaneous control of hand grasping in mice. Andrew Pruszynski will show how first-order neurons in the human skin signal edge-orientation and how these signals could support object manipulation.

Speakers:

Andrew Pruszynski, Western University
Geometric feature extraction in the human tactile periphery

A fundamental feature of first-order tactile neurons is that their distal axon branches in the skin and forms many transduction sites, yielding complex receptive fields with many highly sensitive zones. The functional consequences of this spatial arrangement are largely unknown. Here I provide evidence, based on single neuron recordings in humans, that this arrangement constitutes a peripheral neural mechanism for signaling the geometric features of touched objects. First, I will show that these neurons signal edge-orientation via both intensity and temporal codes. Second, I will show that a neuron's sensitivity to edge orientation can be readily predicted from the spatial layout of its highly sensitive zones. And third, I will describe ongoing work suggesting that people trying to discriminate edge orientation tune their motor actions to optimize edge orientation information arising from their first-

order tactile neurons. These findings reveal that peripheral tactile neurons, like peripheral visual neurons, perform feature extraction computations typically attributed to neurons in the central nervous system.

Michael Hendricks, McGill University
Sensorimotor integration at the subcellular level

Many behaviors require the integration of sensory input with ongoing motor activity. During sinusoidal crawling, the nose of the nematode C. elegans sweeps back and forth, and behavioral studies demonstrate that it is able to detect sensory differences across head sweeps. This information can be used to steer in response to stimulus gradients or correct its trajectory. We have identified a candidate circuit that relies on convergent inputs from head motor neurons and sensory structures on an interneuron pair called RIA. Localized calcium signals within RIA spatially represent – but are not required for – head motor activity, while sensory inputs cause either hyperpolarization or depolarization of the entire neuron. In our model, these two signals are integrated to provide asymmetric feedback to head motor neurons. The circuit's timing mechanism exploits the rate difference between nicotinic (ionotropic) and muscarinic (metabotropic) transduction downstream of cholinergic motor neurons. This compact circuit represents a simple mechanism for converting a spatially-distributed stimulus into a motor bias during navigation.

Katherine Nagel, New York University
Cellular and synaptic specializations for navigation in turbulent odor plumes

Fruitflies – like many insects – are adept at using odor to navigate towards important resources in their environments. Because of turbulence, natural odors form plumes that exhibit complex spatial and temporal fluctuations. These fluctuations constrain the types of algorithms flies might use to find an odor's source. Here I will discuss cellular and synaptic mechanisms at the olfactory periphery that allow fruitflies to extract temporal information from natural odor plumes. First, specializations in peripheral neurons allow flies to encode plume fluctuations as rapidly as possible, given the limits of olfactory transduction. Second, specializations at the first synaptic relay allow the olfactory system to transmit a broad range of signal frequencies to the central brain. We are currently investigating the computational and functional consequences of these specializations using models, genetic perturbations, and quantitative behavioral experiments.

Tuan Bui, University of Ottawa
A class of spinal neurons integrates cutaneous information for motor control

Sensory information is crucial for the proper adaptation of on-going movements to meet the demands of the external world. The spinal cord serves as a main entry point for sensory information from the periphery. Many spinal neurons integrate this sensory information to shape motor activity. Mapping out the involvement of spinal circuits to specific forms of movements is key to understanding how sensory information is used to ensure the proper execution of our movements. A population of spinal interneurons, dI3 interneurons (dI3 INs) can be identified by their expression of the transcription factor Isl1. A combination of genetic techniques, electrophysiology, immunohistochemistry, and behavioural testing were used to show that dI3 INs integrate sensory inputs, notably from low-threshold mechanoreceptors in the skin. A search for the types of motor activity that require dI3 IN participation revealed their role in both hand grasp and locomotor activity. I will describe the degree to which dI3 INs

are involved in these two forms of activity, and in the process, highlight the importance of spinal circuits integrating sensory information to the neural control of movement.

Symposium 5:

Mechanisms of Plasticity

Co-chairs: **Michael Jackson** and **Tabrez J Siddiqui**, University of Manitoba

Overview:

From the simplest invertebrate species to man, mechanisms contributing towards neuronal plasticity are crucially involved in development, enable behavioural adaptations and form the basis for human perception, reasoning, learning and memory. The proposed symposium brings together Canadian experts whose research is focused on elucidating mechanisms responsible for the establishment and maintenance of plasticity. Topics covered will include an overview of studies exploring the signalling requirements for developmental plasticity in zebrafish, the importance of translational control as a determinant of bi-directional plasticity in Aplysia, the use of reverse genetics to elucidate the molecular underpinnings that regulate the form and function of dendritic spines in mice and the mechanisms that guide higher-order plasticity in well-defined circuits underlying odor preference in rats. Note: Session co-chaired by Drs Michael Jackson and Tabrez Siddiqui. Dr Siddiqui is entered as a speaker but will not be presenting.

Speakers:

Wayne Sossin, McGill University
Regulation of eEF2 phosphorylation bi-directionally regulates translation-dependent synaptic plasticity in Aplysia

In Aplysia, distinct training protocols elicit different mechanisms to alter synaptic strength underlying memory formation. In particular, spaced vs. massed training protocols both induce memory formation through activation of protein synthesis, but result in distinct memory traces dependent for their maintenance on persistent PKA (spaced) or PKC (massed). We have found that regulation of eEF2 kinase leading to phosphorylation/dephosphorylation of eEF2 critically distinguishes learning after spaced or massed training. Massed training induces phosphorylation of eEF2 that is required to activate an initiation-independent form of translation from mRNA localized to stalled polysomes. In contrast, spaced training requires de-phosphorylation of eEF2 and regulates translation of distinct transcripts. The implication of these two distinct forms of local translational control for memory formation will be discussed.

Declan Ali, University of Alberta
Synaptic Plasticity at developing Synapses in Zebrafish

Calcium/calmodulin dependent protein kinase 2α (CaMKIIα) and protein kinase Cγ are multifunctional proteins involved a range of plasticity phenomena in developing and adult organisms. In our lab we have

examined the effect of reducing the expression of these proteins on the activity of AMPA and NMDA receptors at developing synapses in zebrafish. We use a combination of single cell, real-time quantitative PCR, immunohistochemistry, behavioral studies and electrophysiology to investigate the expression and role of CaMKII and PKCγ on excitatory synapses associated with large command neurons known as Mauthner cells. Our results show that PKCγ is required for the normal development and expression of GluA2-containing AMPA receptors in developing zebrafish, while CaMKIIα appears to be required for the normal development of NMDA receptors. Our findings pave the way for determining the function of key enzymes involved in synaptic plasticity phenomena at developing synapses.

Zhengping Jia, University of Toronto
Genetic analysis of synaptic and spine plasticity

Synaptic plasticity is a fundamental neural process critical for brain development and function. Dysregulations in synaptic plasticity are closely associated with many neurological and mental disorders. Synaptic plasticity involves both morphological and electrophysiological changes, but how these two processes interact to achieve synapse-specific modifications that are essential for information processing and memory remains poorly understood. We investigate the molecular basis underlying both morphological (spine) and physiological plasticity, by genetically manipulating actin cytoskeleton and glutamate receptors in mice. Specifically we target the Rho family small GTPases and AMPA receptors in the regulation of spine properties and hippocampal long-term potentiation and depression, widely studied models for learning and memory. The most recent results from these analyses will be discussed. Supported by CIHR, NSERC and Sickkids Foundation.

Qi Yuan, Memorial University
Shaping odor coding neuronal ensembles by reward and norepinephrine

How is an odor represented in the brain? How do experience and neuromodulator norepinephrine shape the odor representation? We addressed these questions by assessing activation of the immediate early gene, Arc, using the cellular compartment analysis of temporal activity by fluorescence in situ hybridization (catFISH) technique, which permits visualization of activated neurons by two times of sensory inputs. We found that odor representations in the anterior piriform cortex (aPC) in adult rats were variable, with less than ~30% overlap between the two ensembles representing the same odor. However, if the odor was made behaviorally important by being paired with reward, then the odor representation became more stable. Odor reward pairing also resulted in increased pattern separation between two similar odors. This behaviorally adaptive shaping of odor representations was modulated by norepinephrine. We found that blocking adrenoceptors in the aPC prevented learning of the difficult odor discrimination and refinement of the rewarded odor representation in the olfactory bulb, while adrenoceptor blockade in the olfactory bulb slowed learning and pattern separation in the aPC.

Symposium 6:

Neuroimmunology: A key interface in neurophysiology, neurodegeneration and repair

Chair: **Shalina Ousman**, University of Calgary

Overview:

The immune system plays a pivotal role in maintaining homeostasis in the brain and spinal cord. In addition, immune cells are increasingly found to be involved in the pathogenesis, progression, and/or resolution of diseases and injuries of the central nervous system (CNS) and peripheral nervous system. This symposium will highlight research showing that immune cells such as microglia, T cells and macrophages, and their regulators [Cystatin C (Ousman), chondroitin sulfate proteoglycan (Yong) and ion channels (Schlichter)] promote not only injury but also repair of the CNS during diseases such as Alzheimer's disease (Rivest), multiple sclerosis (Ousman, Yong) and stroke (Schlichter).

Speakers:

Shalina Ousman, Hotchkiss Brain Institute, University of Calgary

Pathogenic immune-mediated mechanisms in multiple sclerosis and its animal model, experimental allergic encephalomyelitis.

Multiple sclerosis (MS) is an autoimmune disease characterized by infiltration of myelin reactive immune cells into the central nervous system (CNS). The disease is associated with the enhanced and down-regulated expression of scores of genes and proteins but the function of most of these molecules is poorly understood. Cystatin C (CysC) is a gene whose level is enhanced in the brains of MS subjects and in the CNS of mice with experimental allergic encephalomyelitis (EAE), a model of MS. CysC is an inhibitor of cysteine proteases and is mostly localized in astrocytes, neurons and macrophages. Because of discordance in the literature regarding its expression in MS patients and its function (neurotoxic vs neuroprotective, pro-inflammatory vs immunosuppressive), we aimed to clarify its role in EAE. Using CysC knockout and over-expressing mice, we found an unexpected gender dimorphism. CysC displayed a detrimental effect in EAE but only in female animals. This female preference was not due to estrogens but was instead attributed to defects in the activation status of antigen presenting cells such as macrophages that subsequently disrupt T cell function.

Sam David, McGill University
Macrophage and microglia plasticity - they are what they eat.

Microglia and macrophages are very plastic cells that can change their phenotype drastically in response to in vitro and in vivo conditions. They can change from pro-inflammatory, cytotoxic cells to anti-inflammatory, pro-repair phenotypes. Although the microenvironment in the damaged or diseased CNS influences macrophage and microglial plasticity, recent work shows that their phenotype is also dependent on what they phagocytose. This presentation will discuss the phagocytosis mediated effects on macrophage plasticity in the context of spinal cord injury.

Serge Rivest, Université Laval
Neuroprotective properties of the innate immune cells.

The CNS is a highly immunologically active organ, with complex immune responses mostly based on innate immune processes. We found that the progressive cognitive decline and decrease in expression of synaptic markers and neurotrophins in the brain of mouse models of Alzheimer's disease (AD) correlated with major changes in the proportions of peripheral blood monocyte subsets. In this regard, low levels of macrophage colony-stimulating factor (M-CSF) were measured in patients with presymptomatic AD or mild cognitive impairment (MCI), which together with low levels of other haematopoietic cytokines predicted the rapid evolution of the disease toward a dementia diagnosis 2 to

6 years later. In addition, injections of M-CSF to AD animal models resulted in benefits in cognition and reduced Aβ levels. It is therefore likely that stimulating monocytic cells may be a new therapeutic avenue for treating AD. We will show new data regarding the potent effects of new molecules to stimulate innate immune cells as a preventive and curative treatment for brain diseases. We will also show the central role, and a possible therapeutic target, of the neurovascular unit in diseases of the CNS.

V. Wee Yong, University of Calgary
Harnessing the benefits of inflammation for repair of the CNS.

Neuroinflammation can be injurious, but an immune response is also required for repair of the CNS. To attempt to elicit reparative inflammation, we examined macrophages exposed to pro-inflammatory (interferon-γ/lipopolysaccharide, iLPS) and anti-inflammatory (IL-4/IL-13) stimuli. Unexpectedly, while iLPS-treated cells killed oligodendrocytes in culture, the addition of LPS to IL-4/IL-13 treated macrophages profoundly enhanced anti-inflammatory responses, and attenuated toxic features. We next inflicted demyelination to the dorsal column of the mouse spinal cord; 3 days after, specific polarizing stimuli were applied once at the site of injury. Four days after that, while the IL-4/IL-13 treatment mirrored controls, the LPS/IL-4/IL-13 animals had significantly increased macrophages with anti-inflammatory properties, and elevated oligodendrogenesis. These beneficial features evolved to improved remyelination measured at 3 weeks post-injury. Our data suggest a new paradigm to elicit CNS recovery, that of simultaneously recruiting both pro- and anti-inflammatory stimulators that integrate their activity to generate reparative macrophages/microglia that enhanced remyelination.

Symposium 7:

Novel Experimental Models of Epilepsy

Chair: **Jesper Sjöström**, McGill University

Sponsored by: *Centre de recherche Institut universitaire en Santé mentale de Quebec*

Overview:

Approximately 60 million people worldwide suffer from epilepsy, a devastating neurological disorder afflicting characterised by recurrent seizures. Despite major recent advances, about 30% of cases cannot be controlled with current therapies, and the key steps by which the healthy brain undergoes epileptogenesis remain unclear. This symposium highlights novel findings in epilepsy research obtained by advances in experimental animal models. These models rely on a range of contrasting approaches, from trauma and ischemia to optogenetics, which enables researchers to focus on different factors that contribute to epileptogenesis.

Speakers:

Peter Carlen, University Health Network
Neocortical ischemia and seizures

Brain ischemia, or sudden lack of perfused oxygen and energy substrates (e.g. hypoglycemia), can precipitate acute seizures, which, when occurring in metabolically impaired tissue, can extend the area of tissue damage by further using up local energy sources. We model focal neocortical ischemia in the mouse somatosensory cortex in vivo, while measuring local field potentials and the extracellular [K+], with local injection of the potent vasoconstrictor Endothelin 1 (ET-1), which reproduces the vasoconstriction and subsequent reperfusion seen clinically. Local electrographic seizures occur in the acute post-ischemia phase (1-2 hours) accompanied by an increase of ~10mM in the extracellular [K+]. ET-1 also blocks astrocytic connexin43 gap junctional communication (GJC), which is required for extracellular [K+] redistribution, but this increase in extracellular neocortical [K+] from GJC blockade was not sufficient to generate seizures. We hypothesize that local ischemia deprives neurons and astrocytes of metabolites (i.e. oxygen and glucose), generating local seizures (by several putative mechanisms), which in turn extend the core infarct.

Aylin Reid, University of Toronto
Electrophysiological abnormalities during epileptogenesis after fluid percussion injury

Epileptogenesis, the process by which normal brain becomes capable of generating recurrent, spontaneous seizures, is not well understood. Post-traumatic epilepsy (PTE), occurring in up to 50% of survivors of a severe traumatic brain injury, is one of the few causes of human epilepsy where timing of the insulting event is known, and therefore the subsequent period of potential epileptogenesis can be investigated and possibly treated. This makes animal studies of PTE not only relevant as they pertain to an important clinical condition, but they may be one of the best models for studying epileptogenesis as it occurs in humans. We have described pathological high-frequency oscillations (pHFOs) and a new entity, repetitive pHFOs and EEG spikes (rHFOS), after fluid percussion injury in the rat. pHFOs and rHFOS occur early after traumatic brain injury and may be non-invasive biomarkers of epileptogenesis. Later after injury, rats develop focal onset seizures, with increasing epilepsy severity over time. The evolution of seizures in this model, and the link between epilepsy and injury severity, make fluid percussion injury a clinically relevant model for studying PTE and epileptogenesis.

Igor Timofeev, Université Laval
Age dependency of trauma induced epileptogenesis

Penetrating cortical wounds trigger seizure activities within first 1-2 days, and then seizures stop. After the end of acute state the epileptogenesis starts, during which brain excitability changes, but unprovoked seizures are not observer. Epilepsy starts with an appearance of spontaneous unprovoked seizures weeks later. We investigated the age dependency of epileptogenesis in penetrating wound models. Young cats (9-14 month) did not develop epilepsy, while adult cats (>10 years) did. Their epileptogenesis was characterized by increased intrinsic and synaptic neuronal excitability. Young (3 months) and adult (>1 year) old mice showed acute seizures, which stopped after a week in young, but not in adult animals. Using DREAD technology we modified cortical excitability around the traumatized cortex of adult mice. The increase in excitability in areas surrounding undercut cortex prevented epileptogenesis and the decrease in excitability dramatically increased seizures and led to increase seizure related mortality. We conclude that prevention of epileptogenesis requires increase in neuronal excitability of traumatized cortex immediately after trauma. Supported by CIHR and NSERC

Jesper Sjöström, McGill University
Optogenetic kindling as a model of epilepsy

To explore circuit changes that accompany epileptogenesis, we created a novel optogenetic kindling model of epilepsy. We hypothesized that repeated brief high-frequency stimulation (kindling) pathologically rewires circuits by excessive recruitment of Hebbian plasticity. To test this, Channelrhodopsin-2 was expressed in motor cortex of male C57BL/6J mice. Every 48h, awake behaving animals were stimulated bilaterally with 445-nm lasers while EEG and video were recorded. Seizures were not elicited in early stimulation sessions, but gradually emerged in 6 out of 6 animals after ~13 sessions. The number of seizures, their duration and Racine score increased with session, while seizure threshold decreased. An elevated seizure susceptibility persisted after 36 days of no kindling, suggesting long-lasting changes. We argue that the elevated seizure susceptibility is mainly due to circuit plasticity, as immunohistology revealed no appreciable cell loss or glial activation. Because of its good experimental control and high specificity, our model enables systematic exploration of how specific neuronal populations, inflammation, or injury contribute to epileptogenesis. Support: CIHR, NSERC

Symposium 8:

Circuit and systems basis of emotion and emotional learning

Co-chairs: **Sheena Josselyn**, The Hospital for Sick Children and Stephanie Borgland, University of Calgary

Sponsored by: *Ontario Brain Institute*

Overview:

Learning about the environmental cues that predict biologically significant events plays an essential role in survival. Indeed, these emotional memories [either negative (e.g., fear conditioning) or positive (e.g., palatable food, illicit drug or alcohol reward)] may attain a privileged status in memory. Perturbation of emotional learning may underlie pathological conditions including anxiety disorders and overeating. Therefore a greater understanding of the mechanisms mediating emotional conditioning may inform the development of more effective treatments for these disorders.

Speakers:

Maithe Arruda-Carvalho, University of Toronto
Maturation of the Prefrontal-Amygdala circuit and the encoding of fear memories

Early life experiences are crucial at defining cognitive and mental health function throughout life. Childhood and adolescence are the predominant age of onset for the majority of mental disorders, periods in which key brain areas involved in emotional processing, such as prefrontal cortex (PFC) and amygdala are maturing. Anatomical and morphological changes occur in such areas during early life; nevertheless, how these changes affect circuit function and its consequences to the onset of mental illness is currently unknown. Using optogenetics and ex-vivo electrophysiology, we have investigated in C57BL6/J mice how synaptic transmission between PFC and amygdala changes across several developmental stages. We found that PFC projections arrive at amygdala between postnatal days 10 and 15. Changes in inhibition:excitation balance, paired pulse and AMPA:NMDA ratios point towards adolescence as a particularly critical period for PFC-amygdala circuit maturation. Understanding how

brain circuits implicated in mental illness mature will be critical for gaining insight into the etiology of those disorders, a necessary step for designing more targeted and efficient therapies.

Lindsay Naef, University of Calgary
Dysfunction of the orbitofrontal cortex in diet-induced obesity

The orbitofrontal cortex (OFC) is involved in the cognitive control of reward processing. It keeps information online and updates behaviour based on changing reward contingencies. Human studies have demonstrated that obesity is associated with lower behavioural adaptation to reward devaluation. The goal of the present experiments was to examine the function of the OFC and to assess reward devaluation in an animal model of diet-induced obesity. Mice with diet-induced obesity display deficits in reward devaluation. Furthermore, obese mice exhibit decreased inhibitory input onto pyramidal neurons of the lateral OFC measured with whole cell patch clamp electrophysiology. To determine if decreased inhibitory input to pyramidal neurons leads to impairment in reward devaluation in normal weight animals, we expressed an inhibitory DREADD in VGAT ires cre mice. Inhibition of GABAergic inputs to the lateral OFC by clozapine N-oxide (CNO) administration impairs reward devaluation. Together, these results demonstrate that obesity induces neuroadaptations in the lateral OFC to alter the processing of sucrose rewards, such that obese mice continue to value sucrose regardless if hungry or sated.

Thomas Kash, University of North Carolina
Dissecting the role of “”Aversive”” circuitry in Addiction

Drug and alcohol abuse are highly comorbid with anxiety and depression. In keeping with this, a large body of work from multiple laboratories points to the critical role of aversive brain systems in driving behavioral pathologies associated with addiction. The broad focus of my laboratory is to identify how discrete circuits in the brain can drive aversive behavior, and understand mechanistically how alcohol and drugs of abuse can dysregulate these circuits. Our goal is to identify novel circuit based approaches to treat addiction. Here I will discuss recent work that highlights the role of discrete circuits in the brain, centered on the extended amygdala, in driving aversive behavior. Specifically, I will discuss how signaling in a discrete population of neurons that express corticotrophin releasing factor in the extended amygdala can drive both reward related behavior, such as binge-like alcohol consumption, and aversive behavior, such as fear learning.

Sheena Josselyn, The Hospital for Sick Children
Winner-take-all neuronal competition for fear memory encoding

A fundamental goal of neuroscience is to understand how information is encoded and stored in the brain. The physical or functional representation of a memory (the memory trace or "engram") is thought to be sparsely encoded over a distributed memory network. However, identifying the precise neurons which make up a memory trace has challenged for scientists since Karl Lashley's "search for the engram" in the 1950's (Josselyn, 2015; Lashley, 1950; Josselyn, 2010; Josselyn et al., 2015). Moreover, it was not known why one neuron (rather than its neighbour) was involved in a given memory trace. We previously showed that lateral amygdala (LA) neurons with increased levels of the transcription factor CREB are preferentially activated by fear memory expression, suggesting they are selectively recruited into the

memory trace (Han et al., 2007). We, and others, went on to show that these neurons were critical components of the memory network by selectively ablating (Han et al., 2009) or inactivating them (Zhou et al., 2009). These findings established a causal link between a specific neuronal subpopulation and memory expression, thereby identifying critical neurons within an engram.

Symposium 9:

Shedding light on the function of cholinergic midbrain neurons

Chair: **Susanne Schmid**, University of Western Ontario

Sponsored by: *Tucker-Davis Technologies*

Overview:

Neurons of the midbrain cholinergic cell groups Ch5 and Ch6 project to wide-spread areas in the brain and are part of the ascending reticular activating system. The specific function of these neurons have been elusive, due to the fact that bilateral lesions of these neurons are lethal, unless they are performed in a way that allows the brain to compensate. Not surprisingly, functional consequences are then minimal. Transient activation and inhibition of these neurons using optogenetics or DREADDS allow for the first time to probe for their specific function. S. Steidl will present data of cholinergic versus glutamatergic projections to the ventral tegmental area and their crucial role in reward and addiction. G. Felsen reports of the effect of cholinergic projections to the superior colliculus and its importance for selecting orienting responses. E Azzopardi will revisit the long-standing dogma that these neurons mediate sensorimotor gating through descending projections to the brainstem, and C. Van Dort will report about the role of the same cholinergic projections to the reticular formation in inducing and maintaining REM sleep in mice.

Speakers:

Stephan Steidl, Loyola University Chicago
Laterodorsal tegmental nucleus inputs to the ventral tegmental area drive reward

The laterodorsal tegmental nucleus (LDTg) provides parallel excitatory cholinergic and glutamatergic input to ventral tegmental area (VTA). We expressed channelrhodopsin 2 (ChR2) in the LDTg of rats and show that light stimulation of LDTg axons in the VTA elicits dopamine-dependent reinforcement. We next used a place preference paradigm to test the behavioral effects of VTA light stimulation of axons from either LDTg-cholinergic or LDTg-glutamatergic neurons. ChAT::Cre mice, whose entry into a light-paired chamber resulted in VTA stimulation of LDTg-cholinergic axons, spent more time in this chamber across sessions and subsequently showed conditioned place preference for the light-paired chamber. VGluT2::Cre mice, whose entry into a light-paired chamber resulted in VTA stimulation of LDTg-glutamatergic axons, entered this chamber significantly more times than the light-unpaired chamber. However, these mice remained in the light-paired chamber for short time periods, and they did not show a conditioned place preference. We suggest that LDTg-cholinergic and LDTg-glutamatergic inputs to the VTA each may contribute to the net rewarding effects of exciting LDTg axons in the VTA.

John Thompson, University of Colorado
Mesencephalic representations of recent experience influence decision making

Initial work from our lab showed that activity in the pedunculopontine tegmental nucleus (PPTg), a mesencephalic region that provides cholinergic and other input to several nuclei in the action selection network, reflects several task-related variables during a sensorimotor decision-making task. More recently, we have focused on the role of the PPTg in representing recent experience, which is thought to be critical for action selection. We recorded and manipulated PPTg activity in mice selecting actions based on sensory cues and recent trial history. We found that, at the time of action selection, activity of many PPTg neurons reflected either the action on the previous trial, its outcome, or both, and that the strength of this activity predicted the upcoming choice. Further, selectively activating cholinergic PPTg neurons increased the influence of recent experience on action selection. These findings suggest that PPTg input to downstream motor regions provides a simple mechanism for integrating recent experience into the computations underlying action selection.

Erin Azzopardi, University of Western Ontario
The role of mesopontine cholinergic neurons in sensorimotor gating

Sensorimotor gating is a pre-attentive process that suppresses sensory evoked motor responses in favor of an orienting response towards a sensory stimulus. Prepulse inhibition (PPI) of the acoustic startle response is a measure of sensorimotor gating It is hypothesized that the principle mechanism underlying PPI is cholinergic inhibition by the pedunculopontine tegmental nucleus (PPT). To test this, we injected transgenic rats (Chat-Cre) with either a DREADD, optogenetic, or respective control virus into the PPT. During certain trials of PPI testing we replaced the auditory pre-pulse with a light stimulation of the cholinergic cells of the PPT. Optogenetic stimulation of the PPT did not induce PPI, but rather facilitated startle in the ChR2 expressing rats. This facilitation was most robust at the ISI of 15 ms, and could be blocked by a nicotinic antagonist. Conversely, chemogenetic inhibition of the PPT did not disrupt PPI at different prepulse levels or interstimulus intervals tested. A trend toward reduced baseline startle was observed, however. Our results suggest that the cholinergic cells of the PPT may not be as critical for PPI as generally assumed.

Christa Van Dort, Harvard Medical School
Activation of cholinergic neurons in the PPT and LDT induces REM sleep

Rapid eye movement (REM) sleep is a critical component of restful sleep, yet the mechanisms that control REM sleep are incompletely understood. Brainstem cholinergic neurons have been implicated in REM sleep regulation but heterogeneous cell types in the area have made it difficult to determine the specific role of each population leading to a debate about the importance of cholinergic neurons. In this talk, I will present data that aims to clarify this question by selectively activated brainstem cholinergic neurons to determine their role in REM sleep regulation. We found that activation of cholinergic neurons during NREM sleep increased the number of REM sleep episodes but not REM sleep duration. To help determine the firing pattern of neurons in the mouse PPT, we also characterized single neuron activity in the PPT across sleep and wakefulness. Our data demonstrate that brainstem cholinergic neurons are important modulators of REM sleep and clarify their role in REM sleep initiation.

Symposium 10:

Nociceptive Circuits: From Molecules to Behaviour

Chair: **Steven Prescott**, The Hospital for Sick Children

Overview:

Understanding the specific anatomical and functional wiring of sensory circuits transmitting touch and pain information is a fundamental challenge in neuroscience. Recent transgenic mouse technology combined with advancements in optogenetics/pharmacogenetics, functional imaging, anatomical and analytical techniques now provide an unprecedented detailed and dynamic view of complex neural networks. In this symposium, we will discuss how we have combined such techniques to understand the workings of the circuitry of the spinal cord involved in nociception (pain). Attempting to bridge the gap between our understanding of the cellular connectivity, network activity and pain perception, the symposium will focus on 4 major questions: 1) What are the molecular pathways underlying the proper development of nociceptive somatotopy? (AK) 2) What do we learn from the optogenetic and chemogenetic control of pain pathways? (PS) 3) How do interneurons in touch-processing circuits gate pain? (RSN) 4) How spinal networks process information and how that processing impacts pain perception? (SP)

Speakers:

Artur Kania, IRCM
A genetic and functional analysis of nociceptive somatotopy

Somatotopic organisation allows the localisation of sensory stimuli relative to the body of the animal. This is particularly important in the context of noxious stimuli whose accurate location is required for survival. In vertebrates, nociceptive signals are sent from sensory neurons to dorsal spinal cord or trigeminal nuclei neurons, and then on to the sensory cortex via the thalamus. The spinothalamic (STT) projection neurons in the spinal cord and their terminals in the thalamus form somatotopic maps, but their importance for nociceptive stimulus localisation is not clear. Using a Cre driver transgenic mouse line, we have generated a spinal-cord specific knockout of a commissural axon guidance receptor. Axonal tracing experiments reveal that in such mice, some STT neurons inappropriately innervate the ipsilateral thalamus. Unilateral noxious stimulation applied to the limb of such mutants elicits behavioural responses suggestive of abnormal left-right localisation of pain. We are currently studying the laterality of thalamic and cortical neuron activities in such mutants, and elucidating the anatomy of STT connectivity.

Philippe Séguéla, McGill University
Selective functional control of peripheral somatosensory neurons in pain circuits

Selective activation or inhibition of peripheral nociceptors allows to control pain transmission and modulate pain perception in preclinical models. Using non-invasive optogenetic stimulation and DREADD-based chemogenetic sensitization of peripheral nociceptors, we show that we can recapitulate key mechanisms of peripheral sensitization and central plasticity that lead to chronic pain. We also

generated novel transgenic mouse lines in which optical activation of the inhibitory proton pump archaerhodopsin-3 (Arch) efficiently silenced the activity of nociceptive C-afferents. Acute and prolonged transdermal illumination of the hind paws of Nav1.8-Arch+ mice reduced mechanical allodynia and thermal hypersensitivity under inflammatory and neuropathic conditions, underlining the critical role of peripheral neuronal components in the development and maintenance of chronic pain. These functional approaches are currently applied to interrogate in vivo the potential contribution of subsets of genetically-identified somatosensory neurons involved in touch, itch or mechanical nociception to pathological pain conditions. Supported by CIHR, NSERC, LAEF, QPRN.

Reza Sharif Naeini, McGill University
Dorsal horn parvalbumin inhibitory neurons act as gate-keepers of touch-evoked pain after nerve injury

Neuropathic pain is a chronic debilitating disease that results from nerve damage, persists long after the injury has subsided. It is characterized by spontaneous pain and mechanical hypersensitivity. Although loss of inhibitory tone in the dorsal horn of the spinal cord is a major contributor to neuropathic pain, the molecular and cellular mechanisms underlying this disinhibition are not fully understood. We have demonstrated that a subset of inhibitory interneurons, containing the marker parvalbumin, prevent touch inputs from activating pain circuits. Our results indicate that parvalbumin interneurons are modality specific filters that gate mechanical but not thermal inputs to the dorsal horn and that increasing parvalbumin interneuron activity can attenuate the mechanical hypersensitivity that develops following nerve injury. Our data indicate that approaches aimed at increasing the activity of these neurons may be beneficial in the treatment of neuropathic pain in patients.

Steven Prescott, The Hospital for Sick Children
Disruption of circuit-level pain processing by chloride dysregulation in spinal dorsal horn

Symptoms of neuropathic pain arise from abnormal processing of somatosensory input. Reduced synaptic inhibition within the spinal dorsal horn is a major contributing factor. Disinhibition arises in large part from chloride dysregulation caused by hypofunction of the potassium-chloride co-transporter KCC2 but it remains unclear how such changes alter sensory processing at the circuit level. Here we show that chloride dysregulation does not render inhibition paradoxically excitatory but does unmask vast amounts of subliminal excitation. Because excitatory interneurons receive more subliminal excitatory input than do inhibitory interneurons, they are disproportionately affected by disinhibition despite both cell types experiencing equivalent chloride dysregulation. Consequently, mechanical allodynia arises when spatial summation of low threshold inputs by excitatory interneurons and downstream projection neurons is dramatically increased upon circuit-wide changes in chloride regulation.

Symposium 11:

Mechanisms governing cerebrovascular structure and function in health and disease

Chair: **Ian Winship**, University of Alberta

Overview:

The cerebrovasculature is a critical component of a properly functioning nervous system. All aspects of the cerebrovasculature, from structural elements like the blood-brain barrier, to functional coupling of blood flow with neural activity, are tightly regulated and controlled in the healthy brain. In small and large vessel disease states such as ischemia, diabetes, vascular dementia or Alzheimer's disease, the mechanisms that govern cerebrovascular structure and function can go awry, which has profound implications for the maintenance of, or recovery of sensory, motor and cognitive abilities. The proposed symposium brings together 4 Canadian scientists actively exploring these fundamental issues. First, Dr. Grant Gordon (Calgary) will discuss his latest research imaging the cellular and molecular mechanisms of tonic astrocytic control of cerebral blood flow. This will be followed by Dr. Edith Hamel (McGill) who will describe how the coupling between sensory-evoked neuronal activity and cerebrovascular responses is affected by acute changes in brain states and by chronic loss of cholinergic neuromodulation. Third, Dr. Craig Brown (Victoria) will reveal with longitudinal imaging approaches, how vascular networks in the healthy and disease-affected brain modify patterns of blood flow or structure to deal with micro-vessel obstructions. And finally, Dr. Andy Shih (MUSC, USA) will describe how matrix-metalloproteinase secretion from pericytes regulate blood brain barrier opening during ischemia.

Speakers:

Craig Brown, University of Victoria
Imaging microvessel recanalization and remodelling following occlusion

The cerebral microvessel bed is an important site for oxygen and nutrient exchange, but is also a low flow system prone to spontaneous stalls and occlusions. While studies have examined larger arterioles, little is known about how microvessels deal with transient or prolonged obstructions and what the long term consequences may be. We used longitudinal 2-photon imaging to track microvascular adaptations to either natural stalls or occlusions induced with 4μm beads. In general, the majority of occlusions were resolved within 12h, while a small percentage were persistent, lasting for days. Microvessels with prolonged occlusions either eventually cleared the emboli or were pruned in a cell death independent retraction sequence reminiscent of development. Surprisingly, a significant portion of vessels that had cleared an emboli and restored flow, still underwent retraction at a later time point. Conceivably these occlusions and delayed pruning events could contribute to the decline in capillary density associated with aging and dementia. Ongoing studies are investigating the mechanisms of microvessel pruning and the impact of vascular disease (diabetes) on microvascular adaptations.

Grant Gordon, University of Calgary
Blood Flow Control Across a Spectrum of Brain Activity States

Using two-photon Ca2+ imaging in ex vivo and in vivo preparations, our recent discoveries indicate that astrocytes use their resting Ca2+ activity to set steady-state arteriole diameter in order to regulate basal brain blood flow - a phenomenon we have termed tonic control. This is a new concept in neurovascular coupling because this form of ongoing arteriole regulation by astrocytes is independent of short-term changes in synaptic activity. We have expanded this framework further by demonstrating neurons are responsible for transient, phasic increases in blood flow in response to rapid changes in neural activity, in a manner that is independent of astrocyte Ca2+ when blood flow is modulated on short timescales. Our ongoing work investigates the conditions under which phasic blood flow control by neurons and

tonic control by astrocytes interact and/or change efficacy. Learning the cellular mechanism of blood flow regulation over a spectrum of brain activity states will be important for understanding its dysregulation in aging or disease, as well as for the correct interpretation of fMRI data.

Edith Hamel, McGill University
Hemodynamic signals: how reliable are they to map changes in neuronal activity?

Changes in cerebral blood flow (CBF) are spatially and temporally coupled to changes in neuronal activity, a process known as neurovascular coupling (NVC) that forms the basis of several brain imaging techniques. It is unclear how reliable this coupling remains during altered brain states and in pathological conditions. Using the whisker-to-barrel pathway as a model of NVC, we found that whisker-evoked changes in CBF and neuronal activity (LFPs and band-limited power) were affected by changes in brain states induced by varying the levels of acetylcholine (ACh), a potent modulator of cortical activity. Under high ACh tone, hemodynamic and neuronal responses were potentiated despite no change in the neuronal network recruited within the activated barrel. Inversely, chronic ACh deprivation compacted the activated barrel and reduced both sensory-evoked hemodynamic and neuronal responses. These findings indicate that hemodynamic signals dependably reflect changes in the activity of the neural circuit underlying sensory processing under altered brain states and in conditions of an ACh-deprived network, as seen in Alzheimer's disease. Funded by CIHR and the Heart and Stroke Foundation.

Andy Shih, Medical University of South Carolina
The Double Life of a Cerebral Pericyte

Pericytes are a key component of the neurovascular unit and well established as builders and custodians of normal blood-brain barrier function. However, their role during ischemia has remained elusive. Our studies using in vivo two-photon microscopy revealed that the "bump on a log" cell bodies of cerebral pericytes were a locus of augmented vascular leakage during capillary ischemia. Unlike their extensive processes that cover the majority of capillaries, pericyte cell bodies are only present along ~7% of total capillary bed. As a result, a disproportionate amount of leakage occurred within the restricted fraction of the capillary bed occupied by pericyte cell bodies. In vivo imaging of matrix metalloproteinase activity further revealed that pericyte cell bodies were sites of intense proteolytic activity following cessation of capillary flow. Thus, pericytes may either directly or indirectly contribute to a heterogeneous form of capillary damage during stroke and related diseases involving microvascular flow impairment. I will discuss possible mechanisms leading to pericyte-associated vascular leakage, and its potential implications on brain injury and repair.

Symposium 12:

Temporal sequences in brain and memory

Chair: **Kaori Takehara-Nishiuch**, University of Toronto

Sponsored by: *Centre de recherche Institut universitaire en Santé mentale de Quebec*

Overview:

The ability to temporally organize the sequence of events is required for extracting meaning from experiences and guiding adaptive behaviour in the future. Past investigations highlighted the role of the hippocampus in remembering the flow of events in distinct experiences and the role of prefrontal cortex in using the memory to organize behaviour in time. This symposium reviews recent studies in animals and humans that examined how neurons in these regions represent the temporal sequence of events and how these regions work in concert with other regions to connect temporally disparate events. These findings provide a new insight into how the brain processes temporal sequences, an evolutionary foundation for many cognitive phenomena, including episodic memory, working memory, and goal-directed behavior. This, along with disruptions of temporal sequence processing in various mental disorders, should make this symposium attractive and informative for both basic and clinical researchers across many research topics.

Speakers:

Howard Eichenbaum, Boston University
Time cells in the hippocampus

The hippocampus is essential to episodic memory, which is characterized by our ability to recall the temporal organization of events that constitute a specific past experience. An understanding of how the hippocampus supports episodic memory would benefit by using an animal model to identify neural coding mechanisms for the temporal organization of memories within the hippocampus. I will present evidence that the hippocampus is critical for memory of order of events in unique experiences in animals, as it is in humans. Furthermore, I will describe recent evidence that hippocampal "time cells" (as contrasted with the famous hippocampal "place cells") encode specific moments in the course of temporally extended experiences, and time cell ensembles encode specific memories and predict memory success. I will also discuss recent evidence on the origins of temporal firing patterns in the hippocampus. These findings support an emerging view that the hippocampus serves episodic memory by creating a scaffold for the organization of events within their spatial and temporal context.

Kaori Takehara-Nishiuchi, University of Toronto
Prefrontal time code underlying temporal associative memory

Many cognitive phenomena such as episodic memory, working memory, and goal-directed behaviour rely on the ability to link information across time. Previous work on the medial prefrontal cortex (mPFC) of rodents suggests that this region is important for learning associations between temporally discontiguous events. To address neuronal substrates for this function, we examined activity of mPFC neurons while rats associated a neutral stimulus with aversive stimulus presented after temporal delays. We found that some neurons sustained firings during intervals between the paired stimuli while other neurons preferentially fired during a specific moment within the intervals. An ensemble of the latter neurons formed a sequential firing pattern which signaled relative time from the preceding stimulus to the expected aversive outcome. In parallel, the amplitude of theta and beta activity ramped up during the intervals. The artificial induction of these oscillatory states with a chemogenetic manipulation enabled association formation over intervals longer than rats can normally learn. Thus, the mPFC uses multiple coding schemes to accurately encode temporally structured experiences.

Nandakumar Narayanan, University of Iowa
Prefrontal dopamine and temporal control of action

The ability to control actions in time is a central feature of mammalian behavior. Humans with diseases involving dopamine have impaired temporal control of action. We study this problem in humans and in rodent models. First, humans and rodents with disrupted midbrain dopamine have impaired temporal control. A key area for temporal control of action is the medial frontal cortex. We pharmacologically and optogenetically manipulated medial frontal dopamine receptors and found that D1 dopamine receptors in the medial frontal cortex are critically involved in temporal control and in temporal processing by medial frontal neuronal ensembles. Specifically, we found that disrupting cortical dopamine receptors attenuated low-frequency rhythms and low-frequency coupling with medial frontal neurons. We used this information to stimulate medial frontal neurons expressing D1 dopamine receptors or thalamocortical projections to medial frontal cortex. D1 or thalamocortical stimulation could compensate for disrupted dopamine and improve temporal processing by frontal neurons as well as timing behavior. These data could illuminate new therapeutic strategies for human disease.

Liang-Tien Hsieh, University of California in San Diego
Temporal representation in the episodic recollection network

Episodic memory entails our ability to mental time travel to the past to re-experience past events. While most of the studies in human episodic memory have focused on memory for what had happened, the neural basis underlying memory for "when" events had happened remains largely unexplored. Existing evidence in humans have shown that the medial temporal lobe, including the hippocampus, parahippocampal cortex, and perirhinal cortex, and a network of cortical regions, including the retrosplenial cortex, angular gyrus, and medial prefrontal cortex, are important for memory functions. However, the extent to which these brain regions support memory for time remains poorly understood. In this talk, I'll present some data from our lab that aim to probe the contributions of these brain areas to memory for temporal information using a sequence retrieval paradigm. The results showed qualitatively distinct contributions of these brain regions to memory retrieval for object sequences, and point to a unique role of the hippocampus in representing events in temporal context.

Monday, May 30, 2016

A - Development

1-A-1 Gene expression profiling in the prenatal brain of Cyclooxygenase-1 and -2 knockout mice - a model system for Autism Spectrum Disorders

Eizaaz Ahmad[1], Ravneet Bhogal[1], Hongyan Li[1], Dorota Crawford[1]
[1]York University

Lipid mediators such as prostaglandin E2 (PGE2) are key molecules important for the development and function of the brain including dendritic spine formation and synaptic plasticity. Abnormalities in the PGE2 signaling pathway due to genetic or environmental causes are linked to Autism Spectrum Disorders (ASD). The objective of this study is to characterize the role of PGE2 during prenatal brain development and how it may lead to autism. We use mouse models with non-functional Cyclooxygenase-1 or 2 (COX1 or 2) which are essential enzymes required for PGE2 production, and thus down-regulated PGE2 levels. Mouse WG-6 V2 BeadChip (Illumina) microarrays were used to determine global gene expression from male mice lacking either enzyme during embryonic days 16 and 19 (E16 and 19). Bioinformatics tools including Venny 2.0, DAVID and AutDB were used to create venn diagrams, carry out functional analysis and determine ASD associated genes, respectively. Selected developmental genes were validated using Quantitative real-time Polymerase Chain Reaction (Q-rtPCR). Our results show that the E16 stage has significantly higher number of affected genes and pathways in both knockouts compared to E19. We also identified a number of genes associated with ASD within each affected pathway. We found differentially expressed Wnt-related genes exclusively in the COX-2-/- mice at E16. This novel prenatal transcriptome profile provides important evidence for the role of the COX-PGE2 signalling in brain development and ASD pathology.

1-A-2 Rescue of neuroanatomical impairments following Mecp2 reactivation in adult mice

Rylan Allemang-Grand[1], Leigh Spencer-Noakes[2], Jacob Ellegood[2], Brian Nieman[2], Jason Lerch[2]
[1]University of Toronto, [2]Hospital for Sick Children

Rett syndrome is a neurodevelopmental disorder caused by mutations in Mecp2. Interestingly, reactivation of Mecp2 leads toa rescue of the neuronal and behaviour impairments in adult mice. Although these findings are exciting, these studies quantified rescue in a limited number of brain regions and restricted their analyses to a few time points. However, to fully understand the dynamics, we scanned mice longitudinally with MRI to determine the regions affected by Mecp2 silencing and spatial changes that occur following Mecp2 reactivation. At P50, male mice were scanned in vivo with MRI, followed by 4 weeks of treatment with tamoxifen to reactivate Mecp2. At P80, a follow up MRI scan was conducted. The acquired images were aligned using a series of iterative linear and nonlinear registrations steps. The Jacobian-determinants were extracted from the deformations fields and used as the dependent variable in the statistical analyses. At P50, mice carrying a silent copy of Mecp2 had a 11% reduction in total brain volume compared to WT. These mice had continual atrophy leading to 3.8% decrease in brain volume by P80. However, mice with a reactivated copy of Mecp2 showed volumetric growth across many regions leading to a 1.5% increase in brain volume. A significant interaction was found within many brain regions involved in motor process and control as well as respiration. Our results demonstrate that Mecp2 mice have volumetric differences across many brains networks early in adult life. However, following Mecp2 reactivation, a drastic volumetric rescue occurs across the brain.

1-A-3 Examining the lineage potential of a novel population of OCT4 expressing primitive neural stem cells in the postnatal brain

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The adult mammalian brain contains two populations of neural stem cells (NSCs). Definitive NSCs (dNSCs) are multipotent, self-renewing, and contribute to ongoing olfactory bulb neurogenesis. More recently, a novel primitive (p)NSC has been identified. This pNSC lies upstream of the dNSC and is able to repopulate the dNSC pool upon ablation. The pNSCs are found throughout embryonic development and persist into adulthood. Interestingly, pNSCs express the transcription factor OCT4, which is a marker for pluripotency and are able to contribute to blastocyst formation. Herein we asked whether the pNSCs found in the brain have the potential to generate cells outside the neuroectodermal lineage, despite residing in the CNS. We used (1) an in vitro embryoid body (EB) assay, a well established assay for examining cell lineage potential and (2) an in vivo teratoma assay which is the gold standard for examining cell lineage through tumour formation. pNSCs were isolated from postnatal and adult brains and used in the in vitro and in vivo assays. Embryonic stem cells (ESCs) were used as positive controls and dNSC derived colonies (OCT4 negative) were negative controls for the experiments. Initial studies have revealed pNSC ability to form EB-like colonies with formation frequency of 60% while dNSCs do not form EBs. Upon differentiation, our preliminary data suggests pNSC-derived EBs give rise to mesodermal cells. These early findings support our hypothesis that brain derived pNSCs are not restricted to neural lineages but instead, may have pluripotent potential.

1-A-4 A Neurodevelopmental and Behavioural Study of Mice Following In Utero and Early Postnatal Exposure to Imidacloprid, a Neonicotinoid Pesticide

Andrew Burke[1], David Hampson[1]
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Imidacloprid (IMD), a neonicotinoid insecticide, is the most widely used insecticide on the planet. Imidacloprid, like nicotine, is a nicotinic acetylcholine receptor agonist. It is imperative to identify any potential effects this chemical may have on animals, as imidacloprid is used on over 140 different crops, most of which are grown for human consumption. The purpose of this study is to examine the behavioural and biochemical effects of chronic in utero and early postnatal IMD exposure. Our treatment regimen entails a chronic exposure whereby pregnant mice are infused with 0.5mg/kg/day of IMD via a subcutaneous osmotic mini-pump, from gestational day 3 to postnatal day 21. Beginning on postnatal day 42, the offspring are studied in a series of behavioural tests assessing locomotor activity, anxiety, social aggression, sensorimotor gating, depression, impulsivity and attention. Previous work, mainly conducted in insects, has suggested that neonicotinoid exposure can lead to a defective cell-mediated immune response. Other studies have reported that imidacloprid exposure can result in permanent defects in the reproductive system of both males and females. Therefore, our biochemical analyses will include tests that will observe sperm abnormalities, immune response abnormalities, and abnormalities in the cells found in whole blood. We anticipate that the results of this study will shed light on the effects of chronic fetal and early postnatal exposure to this heavily used neonicotinoid pesticide.

1-A-5 Embryonic Sim1 expression establishes a patterned V3 neurogenesis profile and subsequent functional separation of V3 subpopulations

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V3 interneurons (INs) in the spinal cord are a major group of excitatory commissural INs that are essential in establishing a robust and balanced locomotor rhythm during walking. In the early embryonic mouse spinal cord, V3 INs arise from the most ventral progenitor domain, p3, as marked by the expression of transcription factor (TF), Nkx 2.2, and then express TF, Sim1 entering the post-mitotic stage. Subsequently, V3 INs migrate dorsally and laterally resulting in anatomically and physiologically distinct subpopulations by postnatal day (P) 0. In order to better understand the developmental mechanisms underlying the separation of V3 subpopulations we investigated their corresponding neurogenesis profiles. The birthdates of V3 INs at P0 were determined by preempted 5-Ethynyl-2′-deoxyuridine (EdU) pulses between embryonic day (E) 9.5 and E12.5, respectively. We found that dorsal V3 INs were born between E9.5 and E10.5 while ventral V3 INs were born later between E10.5 to E12.5. Following this, we investigated the role of Sim1 in establishing the V3 neurogenesis profile and the subsequent physiological differentiation between dorsal and ventral groups. In Sim1 complete knockout mice, a significant difference was observed in the neurogenesis profile of V3 INs. In addition, dorsal and ventral V3 subpopulations were no longer physiologically distinguishable at P0 in the Sim1 mutant. These results suggest Sim1 as an integral factor in determining the specific neurogenesis pattern of V3 INs allowing for proper differentiation and separation of distinct subpopulations.

1-A-6 Early Adolescent Adversity and its Long-Term Effects on Long Evans Rats Aggression-Related Behaviours and Serotonin Fibre Density

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Background: Stress in early adolescence (postnatal day [PD] 22-34) has been found to increase levels of shock-probe burying behaviour in male rats.Male rats that display higher levels of burying in the shock-probe test also display higher levels of attack in the resident intruder paradigm. It has been suggested that these changes are mediated by changes in the serotoninergic system. Objectives: My long-term goal is to develop a translational model of aggression, using the rat as a model organism. In the short-term, my objectives are to: 1. Examine whether early adolescent stress alters aggression-related territorial defense profiles in the rat; 2. Examine whether early adolescent stress alters the neurodevelopment of the serotonin fibres in the hippocampus. Method: In this study we expose male rats to IPS in early adolescence. We measure behaviour in the shock probe test as well as more aggression behaviours in the resident intruder test. We also examine these animals for differences in serotonin fibre density in the hippocampus. Hypothesis: We expect that adult rats with a prior history of IPS in early adolescence will display higher levels of burying in the shock probe test as well as more aggression-related behaviours in the resident intruder test. I expect that early-adolescent stress alters serotonin fibre density in the brain. Implications: These results allow a greater understanding of the effects of early adolescent stress on the neurobiological development of aggression and how neurodevelopment of the 5-HT system. Acknowledgements: Supported by NSERC

1-A-7 Reduced clustered protocadherin diversity alters retinal circuitry

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Proper neural transmission requires that each neuron establish appropriate territories and synaptic partners. To form evenly spaced arbours, some types of neurons exhibit self-avoidance, where neurites of the same cell repel each other by discriminating "self" from "non-self". A diverse set of cell-surface molecules is needed to provide the individual cell-identity required for self/non-self recognition. The clustered protocadherin (Pcdh) locus, with 3 clusters encoding 58 isoforms, provides unique cell identity through stochastic and combinatorial isoform expression. Recently we showed that, deleting gamma-clustered protocadherins (Pcdh-g) disrupts self-avoidance in retinal starburst cells, causing the bundling of self-dendrites. Pcdh-g also promotes survival of some cell-types, but the importance of diversity is not known. Here, we examine the contributions of the alpha-protocadherins (Pcdh-a) in regulating dendrite self-avoidance and neuronal survival in the mouse retina. Removal of Pcdh-a has no affect on survival or self-avoidance, suggesting that Pcdh-a has no role or may be functionally redundant with Pcdh-g. To test this, we used CRISPR to generate a new mouse mutant lacking both alpha and gamma clusters. We found a synergistic loss of retinal cells suggesting that Pcdh diversity is essential for neuronal survival. In parallel we are applying live-imaging approaches to determine the cellular basis by which Pcdhs mediate dendrite self-avoidance. Together, this work will determine the importance of molecular cell-surface diversity in neuronal survival and patterning.

1-A-8 Neural network disturbances in children treated for brain tumors

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Children treated for brain tumors consistently suffer from altered brain structure and function leading to long-term cognitive impairments. These alterations suggest there are also perturbations in the neural networks that underlie cognitive function which can be indexed using functional connectivity. In this study, we aimed to gain insights into how atypical brain networks give rise to cognitive impairment in pediatric brain tumor survivors by examining their resting-state functional connectivity compared to healthy children. We obtained resting-state brain activity using magnetoencephalography, which measures magnetic fields generated in the brain. Time-series were reconstructed for all cortical, subcortical and cerebellar sources in the Automated Anatomical Labeling atlas and filtered into delta (2-3Hz), theta (4-7Hz), alpha (8-12Hz), beta (13-29Hz), low gamma (30-59Hz) and high gamma (60-100Hz) frequency bandwidths. Weighted phase lag index values were computed to compare functional connectivity in pediatric brain tumor survivors relative to controls. We found that following brain tumor treatment, pediatric brain tumor survivors display hyperconnectivity in the delta (2-3 Hz) band compared to healthy children. This atypical network is composed primarily of long-range connections spanning across cortical, subcortical and cerebellar regions. These neural network disturbances in the low frequency range suggest that cognitive deficits experienced by pediatric brain tumor survivors may relate to atypical functional connectivity.

1-A-9 The Effects of Gestational and Lactational Bisphenol A Exposure on Rat Pup Morphological Measurements and on Adrenal Gland Glucocorticoid Receptor Gene Expression

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[1]University of Ottawa

Background Bisphenol A (BPA) is an established reproductive toxicant in animal models and can act on the Glucocorticoid Receptor (GR) to decrease its activity.This study will analyze GR levels in rat pup adrenal glands after perinatal exposure to BPA.Objectives Performance of BPA exposure study in the Long-Evans rat through gestation and up to four days of lactation. Assessment of gross morphological parameters in exposed rat pups post-birth. Characterization of molecular effects of BPA on rat perinatal development through measurement of GR levels in collected adrenals.Methods Long-Evans timed-pregnant dams placed in 5 groups: sucrose vehicle (VEH), positive control (Diethylstilbestrol (DES), 3 low doses of BPA. Dams syringe-fed daily. Pups sacrificed at postnatal day (PND) 5, PND 15. Pup morphometric characteristics (Anogenital Distance (AGD), Crown-Rump (CR) Length, body weight (BW)) recorded on sacrifice day. qPCR reactions performed on male pup adrenals.Results Morphometric analysis showed no interaction effects between the independent variables of sex and exposure ($p>0.05$). Variables then analyzed separately (1-way ANOVA, Dunnets post-hoc to VEH). PND 5: BPA 50 ($p<0.005$), BPA 500 ($p<0.05$) and BPA 50 F groups ($p <0.01$) significantly heavier. CR length significantly longer in BPA 50 ($p<0.05$), BPA 50 F (<0.05) groups. DES ($p<0.005$), BPA 50 F($p<0.005$) groups significantly smaller AGD/CR ratios. No significant effects in PND 15 pups.Conclusions BPA 50 group seems most affected and further analysis required to assess if this translates to GR gene expression differences.

1-A-10 Investigating the role of hnRNP-M in RNA localization during neurogenesis.

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The neocortex is the outermost layer surrounding the cerebral hemispheres of the brain. It carries out some of the most complex cognitive functions such as reasoning and conscious thought. Neurogenesis contributes to the embryonic development of the neocortex. Neural precursor cells (NPCs) divide asymmetrically to expand the pool of neurons, while maintaining their own population. RNA localization contributes to these asymmetric divisions. Heterogeneous nuclear ribonucleoprotein-M (hnRNP-M) is an RNA binding protein that represents a new candidate in the study of asymmetric NPC divisions in the developing brain. Using a murine model of brain development, we have shown that hnRNP-M is expressed during cortical development by both NPCs and post-mitotic neurons. Knockdown studies using shRNA were used to test the hypothesis that hnRNP-M is critical to RNA localization, contributing to the maintenance of NPC divisions. We have found that knockdown of hnRNP-M increases the population of NPCs at the expense of differentiated neurons. Future studies aim to utilize immunoprecipitation to isolate RNA and protein binding partners of hnRNP-M. Identification of these binding partners could provide clues as to the function of hnRNP-M in RNA metabolism. This work aims to demonstrate that hnRNP-M has a significant role in the localization of RNA during neurogenesis. The elucidation of the role of hnRNP-M will provide valuable insight into the molecular basis of brain development, and could have clinical applications for patients with neurodevelopmental disorders.

1-A-11 Development of brain networks after neurodevelopmental insult: the impact of gestational exposure to methylazoxymethanol acetate (MAM)

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Symptoms of schizophrenia, such as hallucinations, psychosis and cognitive impairments, first emerge during adolescence, suggesting the disease has a neurodevelopmental origin. We tested the hypothesis that prenatal insult would result in abnormal brain development using the gestational day 17 exposure

to the mitotoxin methylazoxymethanol acetate (MAM) model of schizophrenia. We measured cytochrome oxidase, a metabolic marker of global, steady-state neuronal activity, in adolescent (35 days old) and adult (70 days old) male control and MAM rats. We quantified cytochrome oxidase activity in the orbitofrontal, prefrontal (PFC), and entorhinal cortices as well as in the dorsal and ventral portions of the hippocampal formation (HF). We did not find any differences between MAM and control rats either during adolescence or adulthood for any region examined. However, functional connectivity, measured by interregional correlations, was significantly different between the ventral HF and PFC in MAM rats compared to control rats at both adolescent and adult ages. The direction of the functional coupling was opposite in adolescent versus adult MAM rats, being negatively correlated during adolescence and positively correlated in adulthood. While we did not detect significant differences in adolescent and adult control rats, the ventral HF appeared less correlated to PFC during adolescence. These data suggest that insult in utero can lead to the development of abnormal ventral HF-PFC function as is observed schizophrenia. This work was supported by: NIH-R01MH084038

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

1-B-12 Using optogenetics to probe neuronal excitability in dissociated dorsal root ganglion neurons

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Our goal was to validate the use of light to probe the excitability of dorsal root ganglion (DRG) neurons to better understand spike initiation. DRG neurons were acutely dissociated from channelrhodopsin-2 (ChR2) expressing mice. Whole-cell patch was used to measure the excitability of these neurons in response to current injection and light (λ=455 nm), and to measure ChR2 conductance density. Our results show that photo-evoked spiking is highly dependent on neuronal intrinsic excitability. The majority of small DRG cells were easily excitable (low rheobase and repetitive spiking) in response to current injection and many responded to light with repetitive spiking. On the other hand, large cells were hard to excite by current injection (large rheobase and transient spiking) and light did not usually evoke spikes in these cells. To validate if photoactivation could be used as a tool to detect changes in neuronal excitability, cell-attached patch recording was used in the presence of inflammatory mediators (IM). Our results show that in the presence of IM, the same light intensity was sufficient to evoke repetitive spiking in cells that previously only spiked transiently. Inflammation had no effect on ChR2 conductance density highlighting that changes in excitability were due to changes in spike initiation mechanisms. Overall, our results show that it is possible to probe excitability of DRG neurons using light. Having validated our technique at the soma, we next plan to use light to test the excitability of other neuronal regions that are prohibitively difficult to patch.

1-B-13 Detecting Gangliosides Expression Profile Changes in Microglial Activation

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With aging, our brains become more susceptible to diseases and injuries. Different brain regions have differing levels of vulnerability to stress and injury, and this brain region dependent variability to vulnerability could be partly explained by the existence of glycosphingolipids within the cell's plasma membrane called gangliosides. Gangliosides are expressed predominantly within the brain and play

various roles within the central nervous system including neural repair, cell survival, and neurodegeneration. Our lab has demonstrated that gangliosides can shift their composition from GM1 back to GM2 and GM3 following stroke in mice and rats indicating a role for simple gangliosides in the neurodegenerative process and this shift may be part of a neuroinflammatory cascade. Based on the literature and preliminary studies conducted in our lab, we hypothesize that GM2 and GM3 gangliosides will increase following microglial activation, while GM1 ganglioside will decrease. BV2 microglia were cultured and activation were induced by LPS and TNF-α for different time points. Immunofluorescence was used to stain for GM1 and GM3 species. ESI-MS was used to quantify the gangliosides expressed within these activated microglia. Both preliminary MS and immunofluorescence results revealed that GM2 and GM3 increased after microglial activation while GM1 decreased. This increase in GM2 and GM3 following activation in vitro support the idea that microglia can be the source of the increase in GM2 and GM3 found in animal models of neurodegeneration.

1-B-14 Still unidentified: The channel driving spreading depolarization during ischemia

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CNS neurons undergo a propagating anoxic depolarization (AD) during ischemia. There is no consensus as to the origin of large inward current driving AD. Various scenarios include excess glutamate release or accumulation, opening of voltage-gated Na channels, or pannexin, ASIC, P2X7 or TRPM7 channels. To address this, we monitored AD in live slices during 10 min of O2/glucose deprivation (OGD) at 34oC, 1) as a propagating increase in light transmittance (LT), and 2) using whole-cell patch recordings from neocortical pyramidal neurons. LT imaging showed an intact propagating AD front despite slice pre-treatment with one of 2 mixtures of blockers in artificial CSF. Blocker `mix 1` contained: 1 uM TTX, 10 mM TEA, 1 mM kynurenic acid, 10 uM nifedipine, 100 uM carbenoxolone/500 uM probenicide [pannexin blockers] and 100 uM picrotoxin. Blocker `mix 2` contained: 100 uM amiloride [ASICs], 2 uM BBG [P2X7], 2 uM FTY720 [TRPM7] and 100 uM CSB [glutamate uptake]. Whole-cell patch recordings from pyramidal neurons showed OGD inducing AD within 5.5 to 8.5 min (n=10). Pre-treatment with `mix 1` merely delayed AD onset (9.2 to 12 min, n=8). `Mix 2` had little effect on onset (6 to 8 min, n=3). Is there a remaining channel candidate that could drive AD? Like OGD, 10-100 nM palytoxin evokes an AD-like event (n=12 slices). And `mix 1` pre-treatment only delays the abrupt depolarization evoked by 100 nM palytoxin in pyramidal cell recordings. Because palytoxin converts the Na/K pump into an open cationic channel, ischemia might elicit a similar conversion that drives AD.

1-B-15 Effects of Pannexin Knockout on Neocortical Neurons in Mice

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Pannexin-1 (Panx1), a protein essential to forming transmembrane channels, has been shown to play a role in modulating neuronal excitability and in acute neurodegenerative changes. The mechanisms by which Panx1 deficiency impairs ionic transport remains unclear. Through quantitative analysis of electrophysiological characteristics of Panx1 knockout mice, including comparison of IV-curves, IH current, and spontaneous inhibitory and excitatory post-synaptic currents, new evidence into the function of this protein is presented. Using whole-cell in vitro patch clamp recordings of cortical cells from layers II & III of both wildtype mice and their Panx1-deficient counterparts, cellular properties are contrasted. This study has revealed hyperpolarized resting membrane potentials and increased action

potential adaptation ratio in the knockouts, demonstrating reduced excitability in Panx1-null mice. This suggests that Panx1 plays a role in maintaining neuronal excitability, and may be of interest in pathological hyperexcitability. Further studies in hyperexcitable conditions, such as through the use of K+ channel antagonists in the extracellular medium, could identify other quantifiable differences of the Panx1 knockout strain. This research provides a valuable tool for understanding the importance of Panx1 in physiological conditions, and quantifies its effects on neuronal excitability. Supported by CIHR and NSERC.

1-B-16 Dynamic interaction between Cav3 channels and calmodulin triggers a second messenger cascade of CaMKII and CREB activation

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Calmodulin (CaM) is known to associate with high voltage-activated calcium channels to activate a cascade of second messenger systems that involve specific calcium sensors. Low voltage-activated Cav3 calcium channels have the important role of responding to subthreshold excitatory events, but were not thought to be regulated by CaM. We find a constitutive association between CaM and the Cav3.1 channel C-terminus under resting calcium conditions, as shown by coimmunoprecipitation in rat brain and tsA-201cells, and imaging of Foerster Resonance Imaging Transfer (FRET) in tsA-201 cells. Calcium influx then promotes a dissociation of CaM from the channel, followed by activation of áCaMKII, as shown by formation of GFP-áCaMKII aggregates in the cytoplasm within seconds. CaMKII aggregates then exhibit translocation towards peri-nuclear regions with activation and phosphorylation of CREB in the nucleus within 1 min. Moreover, áCaMKII and CREB activation can be evoked in tsA-201 cells, mouse hippocampal cultures, and Purkinje cells of rat cerebellar tissue slices with brief exposure to high K+ medium under conditions when all calcium influx is restricted to Cav3 channels. Our findings thus reveal a dynamic interaction of CaM with Cav3.1 calcium channels that triggers activation of a second messenger cascade that is key to cell functions underlying synaptic plasticity.

1-B-17 Histone acetylation by VPA is associated with melatonin receptor upregulation

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Melatonin is an indoleamine with several neuromodulatory and neuroprotective properties. It mediates many of its effects by its two G protein-coupled receptors, MT1 and MT2, which are widely distributed in the nervous system (J Pineal Res, 2015; 58:397-417). We have shown that the histone deacetylase (HDAC) inhibitor, valproic acid (VPA), induces melatonin receptor expression in cultured rat C6 glioma cells (J Neurochem. 2005; 95:1227), and in the rat brain (Int J Neuropsychopharmacol. 2012; 16:1). Blockade of the MAPK pathway does not prevent MT1 induction by VPA, while the HDAC inhibitor, trichostatin A (TSA), mimics its effects on MT1 upregulation in C6 cells (Eur J Pharmacol. 2008; 289:45). In this study, we present evidence to suggest that an epigenetic mechanism, involving histone hyperacetylation of the MT1 promoter underlies this interaction. HDAC inhibitors of various classifications (i.e. SAHA, TSA, M344) are shown to parallel the effects of VPA on MT1 induction in vitro, while valpromide, a VPA analogue lacking HDAC inhibitory activity, does not. The observed increase in MT1 expression by VPA is matched by an increase in global acetylation, and more importantly, an enrichment of H3 acetylation at the MT1 promoter, indicating that histone acetylation and chromatin

remodelling are a primary mechanism underlying this induction. In addition, a secondary mechanism for VPA, related to the modulation of intracellular kinase pathways and/or transcription factors may be involved in the transcriptional regulation of the MT1 gene.

1-B-18 Molecular characterization and modulation of electrical synapses between neuroendocrine cells

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Electrical synapses, or gap junctions, are composed of paired hemi-channels that allow for the transfer of current by connecting one cell to another. Gap junctions mediate electrical coupling in neurons, where they synchronize spiking and promote rapid transmission, thereby influencing the coordination, pattern, and frequency of firing. In the marine snail, Aplysia calfornica, two clusters of neuroendocrine bag cell neurons use electrical synapses to coordinate a synchronous 30-min burst of action potentials, known as the afterdischarge, to release egg-laying hormone and induce reproduction. In culture, paired bag cell neurons present a junctional conductance that is largely voltage-independent and non-rectifying. During the afterdischarge, PKC is activated, which alters both intrinsic excitability and modestly decreases junctional conductance; yet, we know little of how phosphorylation impacts voltage transfer. We monitored the transfer of presynaptic spike-like waveforms (generated in voltage-clamp) to the postsynaptic cell (measured in current-clamp) before and after PKC activation (by phorbol ester) or gap junction block (by fenamates). In control, presynaptic action potentials evoked postsynaptic electrotonic potentials at both -60 and -40 mV, which were markedly reduced by blockers. Moreover, with PKC activation the presynaptic stimulus consistently elicited postsynaptic action potentials, likely by enhancing excitability. Ultimately, PKC may work to promote spread of the voltage signal during the afterdischarge and facilitate reproduction.

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

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During learning and memory formation, reversible physiological changes within synaptic transmission take place in the nervous system. Functional and structural changes at dendritic spines are believed to be the basis of learning and memory in the brain. Long-term potentiation is a form of synaptic plasticity and is the experimental analogue of learning and memory. LTP consists of early phase E-LTP and late phase L-LTP. L-LTP depends on genes expression and proteins synthesis. The signals generated at the synapse must be transported to the nucleus, where they are converted into changes in gene expression. Little is known about the cellular and molecular mechanisms that transduce signal activated at dendritic spines and synapses to the nucleus. LIM-kinase1 (LIMK1), from the LIMK family of serine/threonine kinases, regulates actin cytoskeleton and play a role in structural synaptic plasticity. Using LIMK1 knockout mice, we have presented evidences that LIMK1 play an important role in synaptic plasticity, learning and memory. We have also shown that LIMK1 regulates long-term memory and synaptic plasticity via the transcriptional factor cAMP responsive element binding protein CREB. Whether LIMK1 undergoes nuclear translocation during synaptic plasticity. Using biochemical analysis and histoimmunochemical methods, we have shown that activation and nuclear translocation of LIMK1

occurs during synaptic plasticity and learning and memory formation. Our research also aims to determine molecular mechanisms and role LIMK1 nuclear translocation.

1-B-20 Identifying protein microdomains in complex three-dimensional astrocytes in situ

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Astrocytes have a highly complex 3-D morphology that includes intricate connections with synapses, vasculature, and other astrocytes. As such, they have a variety of functions; these include trophic and metabolic support of neurons, synaptic development and signalling, control of the microvasculature and co-ordination of neuronal networks. However, it is unclear whether astrocytes possess specialized regions to compartmentalize these functions. Our hypothesis is that astrocytes possess functional microdomains, specialized regions within a cell that contain specific, highly localized proteins necessary for regional specialization and cellular function. To investigate this hypothesis we have combined DiOlistics, a biolistic technique for labelling the complete morphology of individual cells in brain tissue with a fluorescent dye, with immunohistochemistry to label mGluR5, Glt-1 or Kir4.1. We examined the distribution of these proteins within the complex three-dimensional morphology of individual adult murine brain astrocytes using confocal microscopy, and then determined their distribution in three-dimensions using ImarisTM, a 3-D confocal image rendering software. Our preliminary studies suggest differences between the distributions of these proteins among astrocytes from similar brain regions. Kir 4.1 is more homogeneously distributed when compared with mGluR5 and Glt-1, which are more clustered along astrocytic processes. These results suggest that there may be specific regions, or microdomains, along astrocytic processes.

1-B-21 Panx1 modulates glutamatergic transmission by regulating the synaptic ananamide concentration

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Ananamide (AEA) is an endogenous fatty acid which modulates synaptic activity. AEA functions as an endocannabinoid and activates cannabinoid 1 (CB1) receptors to decrease the frequency of neurotransmitter release. AEA is also an endovanilloid, acting as a ligand for transient receptor potential vanilloid 1 (TRPV1) channels, increasing neurotransmitter release frequency. Cessation of AEA activity requires degradation. AEA must be transported into the neuron where its degrading enzyme, FAAH, is located. How AEA is transported and regulated at the synaptic level is poorly understood. We hypothesized that Panx1 acts as an AEA transporter because it is capable of fluxing a variety of signaling molecules. Using electrophysiological recordings of CA1 pyramidal neurons, we bath applied AEA to acute brain slices, which increased the frequency of spontaneous excitatory postsynaptic currents (sEPSC), indicating that AEA can modulate these excitatory synapses. When an antibody that blocks Panx1 (a-Panx1) was included in the patch pipette, increased asynchronous glutamate release following presynaptic stimulation was observed. This was prevented by bath-applied capsazepine, a TRPV1 antagonist. Together, these suggest that Panx1 is capable of fluxing AEA across membranes. To test this, we measured dye influx through single-Panx1 channels using cell-attached recording. AEA reduced fluorescent dye flux through single channels, suggesting competition for Panx1's pore. These results suggest that Panx1 is a synaptic AEA transporter that functions to regulate synaptic AEA concentrations.

1-B-22 Rescuing NMDA receptor hypofunction in a mouse model of schizophrenia: Neurophysiological consequences in prefrontal cortex

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The cognitive deficits of schizophrenia include impaired executive function, attention problems and distractibility. These deficits are not well addressed by current treatments and are disabling in terms of reintegration into the work place and society. The transgenic mouse model of schizophrenia with reduced expression of the NR1 subunit of the N-methyl- D- aspartate (NMDA) receptor recapitulates not only the cognitive deficits, but also increased locomotor activity, stereotypy, impaired sensorimotor gating, and deficits in sociability. Adult rescue of NR1 expression restored normal function on tests of executive function (see Mielnik et al., poster). Since medial prefrontal cortex is central to executive function in mice, here we probe prefrontal neurophysiology after adult rescue of NMDA receptor function. Whole cell patch clamp recordings in acute brain slices showed substantial attenuation of NMDA receptor currents in layer V pyramidal neurons in the NR1 knockdown mice compared to wildtype, and the almost complete restoration of these currents in the conditional rescue mice after cre-recombinase activation. Ongoing work is investigating genotype differences in intrinsic properties, synaptic transmission and excitation-inhibition balance. As existing treatments for schizophrenia fail to restore normal executive function, we aim to understand the neurophysiological changes that accompany the restoration of normal cognitive performance after a lifetime of NMDA hypofunction.

1-B-23 The role of cGMP in regulating postsynaptic structure underlying bidirectional plasticity

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Synaptic structure is modulated by neural activity both positively and negatively, which is crucial for synaptic function. However, the molecular mechanism for regulating these bidirectional structural changes remains elusive. Here, we show the role of postsynaptic cGMP which regulates bidirectional structural plasticity by interacting with cAMP. During synaptic activities such as long-term potentiation (LTP) and depression (LTD) of neurotransmission, a postsynaptic structure called the dendritic spine changes its shape and properties through a process called structural plasticity. We found that postsynaptic cAMP facilitates structural long-term potentiation (sLTP), suggesting the involvement of cAMP signaling in spine potentiation. To study bidirectional structural plasticity, we depotentiated dendritic spines by two-photon caged glutamate uncaging after cAMP-dependent sLTP. We found that the enlarged dendritic spine structure was counteracted by depotentiation, indicating bidirectional structural changes. Since cGMP signaling is involved in LTD, which shrinks the dendritic spine, we next addressed whether postsynaptic cGMP can affect cAMP-dependent sLTP. In order to mimic cGMP production at targeted dendritic spines, we utilized our established two-photon optogenetics and found that cAMP-dependent sLTP was counteracted by optogenetic activation of photoactivatable guanylate cyclase, suggesting an interactive mechanism between them. Using pharmacological inhibition of specific cGMP signaling, we will determine how cAMP and cGMP interact in bidirectional synaptic plasticity

1-B-24 Understanding the structural basis of NMDA receptor activation

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NMDA-type ionotropic glutamate receptors (NMDARs) are a major class of neurotransmitter-gated ion-channel essential for normal brain development and function. Although their slow gating behavior is critical to their role in neuronal circuits, the structural basis of NMDAR gating is still not fully understood. Here we investigated the impact of electrostatic and hydrophobic interactions at the ligand-binding domain (LBD) of GluN1/GluN2A NMDARs using a combination of site-directed mutagenesis, molecular dynamic simulations and single-channel outside-out patch clamp electrophysiology. In contrast to non-NMDARs, NMDARs were more resilient to disruption of either hydrophobic or electrostatic interactions within the LBD. In particular, we observed that GluN1 Y535 regulated both the onset and time course of channel activation whereas GluN2A E530 only affected the time course of activation. While both Y535 and E530 are unique to NMDA receptors, GluN1 contains the K531 residue; a key component of the electrostatic network in non-NMDA iGluRs. When this residue is truncated in NMDARs (K531A), we observed little or no impact on channel function. However, when substituted in combination with the E530S mutation, NMDAR deactivation rates and recovery from desensitization were greatly increased, indicating functional coupling between the two residues. Taken together, our data provide the first description of how cross dimer interactions work together to define the slow gating behavior of NMDARs.

1-B-25 AMPA and kainate receptor auxiliary proteins relieve polyamine block by enhancing polyamine permeation

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Channel block by cytoplasmic polyamines is a common feature of many cation-selective ion-channels. At glutamatergic synapses, polyamines, such as spermine and spermidine, have been well-characterized to act as permeant channel blockers of both AMPA- and kainate-type (KARs) ionotropic glutamate receptors (iGluRs). In each case, the degree of polyamine block is voltage-dependent and dynamically regulated, with two of the most prevalent mechanisms occurring either through changes in receptor subunit composition or by the association of the channel with auxiliary proteins. Interestingly, the auxiliary subunits interact with the C-terminal regions of AMPARs and KARs and these interactions are crucial for the charge-screening mechanism that has been proposed to relieve polyamine block. Recently, we showed that the KAR auxiliary proteins, Neto1 and Neto2, attenuate polyamine block by enhancing blocker permeation through the channel pore. Here, we characterized the rates of polyamine block and unblock at GluA2 AMPARs and found that the auxiliary proteins, gamma2 and CNIH3, indeed relieve polyamine block by increasing blocker permeation, but also by increasing the unbinding rates and lowering polyamine affinity. Ongoing experiments are aiming to determine the structural basis of these effects.

1-B-26 The role of Neuroligin 2 and inhibitory transmission in the function of thalamic circuitry during epilepsy

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Epilepsy is one of the most common neurological disorders. At the cellular level, epileptic seizures are caused by abnormal, excessive or synchronous neuronal electrical activity in the brain. However, the exact mechanisms of epilepsy remain largely unknown. Neuroligin 2 is a postsynaptic cell adhesion protein, which is exclusively located at inhibitory synapses and serves a role in regulating the balance between brain excitation and inhibition. Importantly, the imbalance between excitation and inhibition tends to cause the disruption of neuronal activities, which may lead to epileptic seizures. By using electroencephalogram and electrophysiological recordings, we found that mice lacking Neuroligin 2 display abnormal seizure-like brain activities and an impaired inhibitory neuronal function in an epilepsy-related thalamic circuitry. Importantly, the abnormal brain activity can be rescued by the administration of a drug directed at enhancing the inhibitory synaptic transmission. These results suggest that Neuroligin 2 regulates normal brain function through modulating inhibition. Our findings provide crucial insight into the mechanisms underlying epilepsy generation and to facilitate the understanding and treatment of related brain disorders.

1-B-27 Ca2+-Dependent KCC2 Dephosphorylation as a Mechanism for Inhibitory STDP

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Inhibitory synaptic transmission in the adult central nervous system is chiefly mediated by γ-aminobutryic acid (GABA) binding to the Cl−-permeable ionotropic GABAA receptor. Subsequent Cl− influx, hyperpolarizing the cell, is made possible by maintenance of low intracellular Cl- by the K+-Cl− cotransporter KCC2. Repetitive activation of pre- and postsynaptic neurons leads to altered strength of synaptic signaling, the degree of which depends on the temporal separation between pre- and postsynaptic spikes, a phenomenon known as spike timing-dependent plasticity (STDP). At GABAergic synapses, repetitive activation within ±20ms leads to a depolarizing shift in the GABA reversal potential (EGABA), diminishing the strength of inhibition. It has been hypothesized that this change results from diminished Cl- extrusion capacity by KCC2. It is known that inhibitory STDP involves Ca2+ influx via L- and T-type voltage-gated Ca2+ channels (VGCCs). Furthermore, phosphorylation of KCC2 residues involved in membrane stabilization and transport efficacy are under the control of Ca2+ -sensitive kinases and phosphatases. We proposed that Ca2+ influx via L- and T-type VGCCs affects kinase and phosphatase activation, thereby altering KCC2 phosphorylation and hence Cl− extrusion capacity. We used a kinetic model of KCC2 phosphorylation in silico to show that Ca2+ entry via T-type VGCCs could produce spike timing-dependent changes in KCC2 phosphorylation leading to removal from the membrane, hence intracellular Cl− accumulation and reduced strength of inhibition as observed in inhibitory STDP.

1-B-28 Synaptopodin in Necessary for Homeostatic Synaptic Scaling at CA3-CA1 Synapses

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Synapse strengthening and weakening is considered the biological basis of learning and memory but, when unchecked, can disrupt stable neuronal function. Homeostatic synaptic scaling offsets Hebbian destabilization, where chronic activity perturbations result in compensatory AMPAR content changes at excitatory synapses. Most excitatory synapses contact dendritic spines, and a majority of large spines possess the actin-binding protein synaptopodin (SP). While SP contributes to local protein synthesis, calcium buffering, and Hebbian plasticity, its role in mediating synaptic scaling remains unknown. To understand the functional role of SP in synaptic scaling, we used whole-cell patch-clamp

electrophysiology to record synaptic activity at CA1 pyramidal neurons of organotypic hippocampal cultures. By reducing neuronal activity with tetrodotoxin (TTX) for 3-4 days then recording AMPA-mediated events, we observed that synaptic strengths failed to increase in SP-knock-out (SPKO) cultures unlike in wild-type (WT) cultures. Studies also show astrocytic tumor necrosis factor-alpha (TNFα) as a significant mediator of synaptic scaling and, with growing interest in tripartite synaptic neuronal control, we wanted to see if SP is involved in TNFα-mediated synaptic scaling. Using ELISAs, we found that TNFα levels did not elevate after activity blockade in SPKO cultures unlike in WT cultures. Chronic TTX treatment with soluble TNFR1 to scavenge TNFα also rendered WT cultures incapable of scaling up synaptic strengths. We posit that SP and TNFα operate together to mediate synaptic scaling.

1-B-29 Using Local Field Potential (LFP) modeling to understand inhibitory cellular contributions to network rhythms in hippocampus

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Oscillatory Local Field Potentials (LFPs) are extracellularly recorded potentials 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" a python package that implements this framework is available. Using LFPy, we construct a pyramidal model in CA1 hippocampus to generate computational LFPs. Our pyramidal model receives inhibitory synaptic input from four different types of CA1 interneuron populations and we use our computational LFPs to investigate their contribution to the extracellular field. The inhibitory synaptic inputs used are from a previous, experimentally constrained inhibitory network model developed to understand spontaneous theta (3-12 Hz) rhythms as expressed in an intact hippocampus preparation. In our current model we placed a virtual electrode probe along the vertical axis of the pyramidal cell to record its LFP output in a layer dependent manner. We identified regimes where specific interneuron cell type interactions distinctively affect the polarity, amplitude and frequency of the LFP signal. Each of these LFP regimes was obtained for a discrete number of network states and was used to assess the contribution of different cell types to the recorded LFP in experimental settings.

1-B-30 Cation channel regulation by reactive oxygen species in Aplysia neuroendocrine cells

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Ion channels are essential for regulating the excitability and plasticity of neurons. For example, changes to activity can be brought about by non-selective cation channels (which pass Na+ and K+, and sometimes Ca2+). These channels generate persistent spiking and plateau potentials, which influence learning, sensory coding, motor pattern generation, and neuroendocrine control. The bag cell neurons of the mollusc, Aplysia, have been used extensively to examine the regulation of secretion and excitability. Upon stimulation, these neuroendocrine cells undergo a prolonged afterdischarge during which hormones are released to initiate reproduction. The afterdischarge presents as a prolonged burst of action potentials, and is sustained by the opening of several cation channels, including a Ca2+-

permeable, Ca2+-activated, voltage-dependent cation channel. We tested the effects of reactive oxygen species, in particular hydrogen peroxide (H2O2), on the function of the cation channel. Under whole-cell voltage-clamp recording, micromolar to millimolar concentrations of H2O2 were perfused over cultured bag cell neurons, resulting in depolarization or inward current. Moreover, application of H2O2 at different holding potentials confirmed that this current was voltage-dependent. Interestingly, micromolar concentrations of acetylcholine, the neurotransmitter that initiates the afterdischarge, also caused inward current. This suggests that following opening of cholinergic ionotropic receptors, H2O2 may recruit the voltage-gated cation channel to maintain the afterdischarge.

1-B-31 Electron Microscopy Analysis of Synaptic Vesicle Tethering by Calcium Channels at Presynaptic Active Zones

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Neurotransmitter is released from presynaptic terminals by calcium-gated fusion and discharge of synaptic vesicles (SVs) at active zones (AZ). Based on single-channel gated fusion we predicted that SVs are tethered to N-type (CaV2.2) calcium channels (Stanley 1993). Using a direct, in-vitro binding assay we recently reported that SVs can bind to a 49 amino acid region towards the tip of the CaV2.2 C-terminal (Wong et al. 2013, 2014). Resolving SV tethers in presynaptic terminals have previously required cryo-electron tomography (Siksou et al. 2007). We were able to reveal these tethers using conventional transmission electron microscopy (EM) by imaging synaptosome ghosts in which the cytoplasm that aldehyde-fixation would thicken had been ejected by osmotic rupture (Wong et al. 2014). We observed two classes of links that were related to the distance of the SV from the AZ: multiple-short (<45 nm) or single-long (45-175 nm) tethers. Based on its amino acid backbone we estimated that a CaV2.2 C-terminus could extend as far as ~200 nm into the presynaptic interior and suggested that this corresponds to the single-long tethers. We proposed a model where the SVs are 'grabbed' from peri-AZ cytoplasm by a long G-tether and are then 'locked' (L-tethered) by secondary attachments in preparation for exocytosis. To explore the G-tether hypothesis we used EM immunogold-labelling to localize the C-terminal tips of CaV2.2. Gold clusters were enriched on SVs in the peri-AZ region. These findings provide direct support for the idea that SVs bind to the channel distal C-terminal in situ.

1-B-32 Changes in cation-chloride cotransporter complexes with NMDA receptors following brain trauma

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Inhibitory GABAergic transmission in the mature CNS is dependent on the expression of the K+-Cl- cotransporter 2 (KCC2), a neuron-specific member of the cation-chloride cotransporter (CCC) family. KCC2 uses the K+ gradient to extrude Cl-, thereby maintaining low intracellular Cl- ([Cl-]i) which causes membrane hyperpolarization upon GABA-A receptor activation due to Cl- influx. In contrast, NKCC1 (another CCC family member) is predominantly expressed early in development and uses the Na+ gradient to cotransport Cl- into cells, maintaining high [Cl-]i and thus depolarizing GABAergic currents. Recently, the kainate-type glutamate receptors (KARs) were discovered to interact with KCC2 and regulate its expression and function. Here, we provide evidence for a physical complex formed between NMDA-type glutamate receptors (NMDARs) and CCCs. Additionally we determined that the NMDAR-CCC

interactions are perturbed following penetrating traumatic brain injury (TBI). TBI was modelled using controlled cortical impact in mice. These novel complexes containing excitatory ionotropic glutamate receptors and inhibitory cation-chloride cotransporters suggest the existence of a glutamate-dependent protein complex capable of regulating local neuronal chloride homeostasis, impairments of which could contribute to network dysfunction following TBI.

1-B-33 Aberrant Chloride Homeostasis and Inhibitory Synaptic Transmission in Huntington's Disease

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Proper GABAA-mediated synaptic inhibition requires low levels of neuronal Cl- that is mainly achieved by the K+-Cl- cotransporter, KCC2. When KCC2 expression decreases, the neuronal Cl- gradient collapses and there is a profound reduction in the inhibition-excitation balance that can produce numerous neurological disorders such epileptic seizures. Huntington's disease (HD) is a neurodegenerative disorder caused by mutations in the Huntington protein (Htt). Recently, the in vivo proteomic interactome of Htt revealed that the KCC2 encoding gene, Slc12a5, is highly enriched in the Htt proteome, and this interaction decreases when Htt is mutated (mHtt). Here, we biochemically validated that KCC2 and Htt interact in both COS-7 cells and whole brain lysates from wildtype mice. We also showed that this interaction is reduced in the R6/2 mouse model of HD. In addition, western blot analysis demonstrated that the total KCC2 level significantly decreases in both pre-symptomatic and symptomatic HD brain compared with wildtype brain. To determine whether this reduced interaction results in KCC2 dysfunction and impaired synaptic transmission, we recorded the reversal potential of GABA (EGABA) as an indirect measure of KCC2 function using whole-cell recording and revealed that hippocampal and cortical neurons from R6/2 brain slices have a depolarized EGABA when compared with wildtype neurons. Characterization of the KCC2: Htt interaction could reveal novel molecular targets that can be used to enhance KCC2 function and possibly restore aberrant synaptic transmission in the HD brain.

1-B-34 cGMP-dependent protein kinase regulates synaptic growth and function at the Drosophila larval neuromuscular junction

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The foraging gene in Drosophila encodes a cGMP-dependent protein kinase (PKG). PKG is thought to regulate several aspects of synaptic function, including synaptic plasticity, synaptic vesicle exocytosis and endocytosis, and neurite outgrowth. However, the mechanisms by which PKG regulates these processes are not fully understood. In addition, much of the evidence for its putative role in these processes is based on the use of pharmacological inhibitors. Pharmacological approaches can be limiting because of their non-specific effects and the inability to distinguish between presynaptic, postsynaptic and glial effects. To overcome these limitations, we used a genetic approach to understand the role of PKG. Here, we used a newly created foraging null mutant to characterize the synaptic effects of PKG at the Drosophila larval neuromuscular junction. We found increased nerve terminal growth and increased synaptic transmission in the foraging null mutant. Next, we used RNAi to knockdown foraging selectively in neurons, glia or muscles to determine where PKG was required for these synaptic effects. We found that only glial PKG regulated synaptic growth, whereas presynaptic, postsynaptic, and glial PKG all

regulated synaptic transmission. Overall, PKG negatively regulates both synaptic growth and synaptic transmission.

1-B-35 Activation of AMPA receptor-auxiliary protein complexes is coordinated by distinct structural pathways

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AMPA-type glutamate receptors (AMPARs) are tetrameric, ligand-gated ion channels that mediate excitatory signaling in the mammalian brain. Native AMPARs are typically expressed in association with one or more auxiliary subunits from amongst several protein families. The most thoroughly characterized of these families are the Transmembrane AMPAR Regulatory Proteins (TARPs), which typically help to localize AMPARs at the synapse and positively modulate their function (i.e. prolong activation). Nevertheless, it is presently unclear how TARPs physically interact with AMPARs to bring about changes in gating and ion permeation. Using a combination of patch-clamp electrophysiology, X-ray crystallography, and molecular dynamics simulations, we identify two structural motifs that govern the duration of channel activity for AMPAR complexes. A network of inter-subunit interactions at the apex of the AMPAR ligand-binding domain (LBD) is critical for gating by pore-forming subunits, while a conserved motif at the base of the LBD prolongs activation when TARP subunits are present. Accordingly, channel activity is almost entirely abolished by elimination of the apical network, but restored via auxiliary protein interactions with the lower LBD lobes. In conclusion, we demonstrate that activation of native AMPAR complexes is coordinated by multiple structural pathways in the presence of auxiliary proteins.

1-B-36 Organization of paranode axoglial domain requires the netrin-1 receptor UNC5B

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Netrin-1 and its receptors direct cell migration and axon extension in the developing Central Nervous System (CNS). After development, netrin-1 continues to be expressed in the mature CNS and is involved in multiple aspects of adult brain function, including the organization of oligodendroglial paranodal junctions. Here, we show that expression of the netrin-1 receptor UNC5B is upregulated in the adult mouse brain and is enriched at the paranodes of myelinated axons. Our findings indicate that oligodendrocyte-specific deletion of UNC5B does not alter compact myelin thickness or abundance in vivo. In contrast, in 9 month-old UNC5B knockouts (cKO), compact myelin periodicity is decreased and axoglial paranodes become severely disorganized, with glial loops detaching from the axon. Caspr-1 and Kv1.1 disperse along the axon, consistent with a loss of segregation between specialized myelin domains. Paranodal disruption is less severe in younger, 3 month-old cKOs, indicating that the myelin disruption progressively worsens with age. Our findings reveal a novel contribution of UNC5B to the maintenance of the axoglial apparatus that is required for normal paranode organization in the adult mammalian CNS.

1-B-37 The Effects of Retinoic Acid on Voltage-Gated Calcium Channels in CNS Neurons

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Retinoic acid, the active metabolite of Vitamin A, regulates cellular function by binding to receptors (RARs and RXRs), and can exert both genomic and nongenomic effects within the cell. Retinoic acid signaling is important in spatial learning and memory, and at the cellular level, affects hippocampal long-term potentiation, long-term depression and homeostatic synaptic plasticity. In particular, retinoic acid regulates homeostatic synaptic plasticity by interacting with calcium signaling. We have previously shown that acute application of retinoic acid can affect the firing properties and intracellular calcium levels of cultured CNS neurons, in a dose- and isomer-dependent manner. Voltage-gated calcium channels are a primary source for intracellular calcium and also regulate neuronal excitability. In this study, we thus determined the effects of physiologically relevant concentrations of retinoic acid on voltage-gated calcium currents in cultured CNS neurons. Neurons were cultured in 500 nM of either all-trans or 9-cis retinoic acid and whole-cell voltage clamp recordings were performed 24 hours later. We found that retinoic acid affected the peak current density (carried by barium) in an isomer-dependent manner, providing further evidence that the retinoic acid and calcium signaling systems may interact to alter neuronal excitability or function.

1-B-38 Circadian and homeostatic remodeling of excitatory synapses

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Homeostatic scaling is believed to regulate neuronal firing through global, non-Hebbian, adjustments to synaptic weights while maintaining the information stored through Hebbian plasticity mechanisms. While scaling has clearly been demonstrated in neurons in culture, true physiological functions of homeostatic scaling in vivo are not known. Sleep plays an essential role in normal cognitive functions. Evidence suggests that the benefits of sleep may occur via synaptic mechanisms, including a global weakening of synapses. Using sub-cellular fractionation, biochemistry and quantitative proteomics, we characterized the changes that occur in forebrain excitatory post-synaptic densities (PSD) through the dark/light cycle in mice. During the light phase when mice spend more time asleep we observed reduced levels of synaptic AMPA receptors and reduced AMPA receptor phosphorylation consistent with global synaptic weakening. These changes are driven by the immediate early gene Homer1a which is kept at low levels in the PSD during wake by the neuromodulator noradrenaline. During sleep, Homer1a remodels the mGluR1/5 signaling complex which is important for the consolidation of contextual memory. These findings reveal part of the molecular mechanisms at play during sleep and suggest that the physiological function of homeostatic scaling-down may be to renormalize synaptic strength during sleep.

1-B-39 Enhancement of neuronal excitability as a trigger for memory consolidation in the mollusc Lymnaea stagnalis.

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A fundamental goal of neuroscience is to elucidate the processes that enable long-term information storage in the brain. One approach to this challenge is through understanding what factors determine whether an animal forms the memory of a given experience. In this study, we took advantage of the natural variation in memory formation in an aversive operant conditioning paradigm in the mollusc Lymnaea stagnalis. L. stagnalis are bimodal breathers that, under hypoxic conditions, exhibit an aerial respiration behaviour at the water surface via opening of its pulmonary orifice, the pneumostome.

Learned suppression of this behaviour can be induced by applying a tactile stimulus to the pneumostome upon each attempted opening to elicit its immediate closure. Soma-ablation studies have shown that the singly identifiable giant respiratory pacemaker neuron, the RPeD1, is the necessary site for the formation, reconsolidation and extinction of long-term memory (LTM) in this paradigm. We employed intracellular sharp electrode recordings to characterize the intrinsic and synaptic properties of the RPeD1 during LTM formation. We observed that animals that form LTM exhibited time-dependent increase in neuronal excitability proceeding persistent enhancement of synaptic strength during the first 24 hours after conditioning. These findings suggest that plasticity in neuronal activity may play an important role in determining the fate of nascent memory traces and thus may act in an integrated model of memory formation with synaptic plasticity.

1-B-40 Finite element modelling of Calcium dynamics in dendritic spines

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We use mathematical modelling to better understand the evolution of calcium concentration and electric potential in dendritic spines. Using the technique of finite elements from the field of industrial mathematics and solving the Poisson Nernst Planck equations, we were able to predict changes in calcium concentration and electric potential in the nanometric range which is to our knowledge unprecedented. From our modelling results, we obtained a better understanding of the elusive relationship between the shape and functions of dendritic spines believed to play an important role in signal integration and memory. We tested how the geometries of the spine head and neck affect integration of electrical signals and the cascade of cell signaling triggered by calcium influx. We found that the neck length and radius play an important role in calcium compartmentalization while they have a lesser impact on electrical signaling as the electrical time constant of the spine when considered as an RC circuit is much smaller than the time constant of synaptic events. Moreover we found that interactions between the electric field and ion dynamics in the nanometric Debye layer affects calcium concentration near the membrane which enhances calcium influx triggered cellular signalling. Finally, we showed how our simulations could be used to interpret experimental results from optical measurement of voltage and calcium sensitive dyes.

1-B-41 Cloning of the chick CaV2.1 voltage gated calcium channel

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Transmitter release is gated primarily by P-type voltage-gated calcium channels (CaV2.1) at most mammalian synapses while N-type (CaV2.2) channels play a significant but lesser role. While this is also true in some lower vertebrates curiously in synapses in the chicken transmitter release is gated almost exclusively by N-type (CaV2.2) channels. Our objective is to resolve this dichotomy and in this study we have used a cloning approach to look for, and characterize the primary molecular structure of chick CaV2.1 channels. There were two main clues: a large fraction of the CaV2.1 channel has been predicted for a distantly related bird and second, a small segment of a putative chick CaV2.1 channel exists in GenBank. In addition, during our cloning experiments a larger part of the chick CaV2.1 (NCBI: XP_015129076.1) was predicted that still lacks over a third of the protein, including the N-and C-terminals. Standard and RACE 5'-3' PCR applied to genomic chick cDNA generated a full length CaV2.1 amino acid sequence. Interestingly, while the channel includes the transmembrane domains, the C-

terminal is truncated and lacks a typical DxWC terminus. This sequence also contains a residue critical for ω-agatoxinIVA binding. Thus, we have cloned the first CaV2.1 channel in birds. While we cannot as yet answer the question as to why the channel fails to contribute significantly to the gating of transmitter release in the chick, one possibility is that the truncated C-terminal lacks the signalling domains that are necessary to target the channel to the active zone.

1-B-42 Cholinergic neurotransmission in the substantia nigra pars compacta modulates dopaminergic neuronal activity

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The midbrain dopaminergic (DA) system in the substantia nigra pars compacta (SNc) is a key element in the control of locomotion. Although downstream events in DA striatal signaling has been the subject of intensive research, less attention has been concentrated on how the upstream modulators, including the brainstem cholinergic system, regulate SNc DA neuronal activity. Therefore we hypothesized that the brainstem cholinergic system is a master regulator of DA activity and neurotransmitter release in SNc. We performed whole-cell recordings of SNc DA neurons in brain slices of mice expressing channelrhodopsin in cholinergic neurons (ChAT-ChR2). We recorded from the medial and lateral SNc. We observed that 92% of blue light evoked responses were excitatory in lateral SNc, while in medial SNC 98% of responses were inhibitory. Although 98% of all the evoked responses in lateral SNc were inhibited by nicotinic acetylcholine receptor (nAChR) antagonists, in the medial SNc only 68% of the evoked inhibitory currents were blocked by nAChR antagonists. We hypothesized that there may be a direct release of GABA in response to blue light i.e. some cholinergic neurons also co-release GABA. Using ChAT-tdTomato mice and also AAV1-ChR2 injection into the midbrain of ChAT-cre mice we identified a new population of cholinergic neurons in the midbrain which are positive for GAD67. Together our data suggest that the cholinergic system may regulate the excitability of SNc neurons within a tight range by facilitating both excitatory and inhibitory inputs.

1-B-43 Determinants of the heterogeneous synaptic function at the mature calyx of Held 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 largely 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 single and high-frequency train stimuli-evoked calcium dynamics mediated solely by P/Q-type calcium channels in distinct compartments of different types of calyces. We found calcium transients throughout the entire calyceal arborization, being the largest in the smallest compartments (swellings). AP propagation into small and large compartments was validated by direct cell-attached recordings at different sites of the same calyx. Patch-clamp recordings showed a significantly higher calcium channel density in complex calyces than that in simple ones. Presynaptic injections of slow calcium buffer EGTA attenuated Pr and RRP more robustly in complex calyces. 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.

1-B-44 The Involvement of Satellite Glial Cells in Different Models of Tooth Pulp Inflammatory Pain in Rats

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This study investigated whether different models of tooth pulp inflammatory pain display distinct patterns of glial activation in the trigeminal ganglion (TG) and in association with nociceptive behavior indicated by locomotor changes. The pulps of the left maxillary first molar of groups of male Wistar rats were exposed with a low speed dental drill. In group A, the pulps were left exposed to the oral cavity. In group B, the pulps were exposed and immediately sealed with temporary dental filling. In group C, the pulps were exposed, and 0.2 µl of Complete Freund's Adjuvant (CFA) was applied, followed by immediate sealing of the pulp. Group D comprised naïve rats, as negative control. Body weight, water and food consumption, and locomotor activity in an open-field test were evaluated at 1, 2, 3 and 8 days after pulp exposure. At each time point, animals were euthanized. Ipsilateral and contralateral TGs were removed for immunohistochemical identification of satellite glial cells (labelled with GFAP). There were no statistically significant differences (two-way ANOVA followed by Bonferroni) between groups in body weight gain, food and water consumption. There were significant reductions of locomotor activity at 3 days in group C compared to group D. Immunohistochemical analysis revealed a significant increase in ipsilateral TG of neurons with GFAP-positive satellite glial cells labelling at 3 days in group C compared to group D. This study has shown that pain-like behaviour occur only in rats with CFA-treated pulps and was associated with glial activation in the TG.

1-B-45 The Mistrafficking of Christianson Syndrome-Linked Mutation NHE6ΔES Impairs the Structure and Viability of Hippocampal Pyramidal Neurons

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Christianson Syndrome (CS) is an X-linked neurodevelopmental disorder characterized by intellectual disability, epilepsy, and autistic features that is due to mutations in sodium/proton exchanger NHE6. We have previously shown that in hippocampal neurons, NHE6 localizes to the membranes of early and recycling endosomes, where it functions to regulate luminal pH and glutamatergic AMPA receptor (AMPAR) trafficking in response to activity. This is critical for long-term potentiation (LTP), the neural substrate behind learning and memory that could be impaired in CS patients due to the loss of NHE6 function. Currently, we are investigating one such NHE6 mutant that possesses a deletion of amino acids Glu287 and Ser288 (NHE6ΔES). Overexpression (OE) of NHE6ΔES in primary hippocampal neurons decreased both dendritic arborization and mature dendritic spine density compared to controls. Along the dendrite, NHE6ΔES showed reduced colocalization with endogenous NHE6 and markers for early and recycling endosomes and was instead redirected to lysosomes. Notably, NHE6ΔES exhibited less colocalization with GluA1-positive AMPARs, which must be trafficked properly to synaptic sites following LTP induction. However, both wild-type NHE6 and NHE6ΔES showed little colocalization with GluA2-

positive AMPARs, implying that NHE6 mostly functions during the early phase of LTP. Moreover, NHE6ΔES OE induced cell death in neurons. Overall, we show that NHE6ΔES may result in the CS phenotype through the disruption of vesicular trafficking at excitatory synaptic sites.

1-B-46 Ionotropic and metabotropic kainate receptor signalling regulates KCC2 and synaptic inhibition

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Potassium-chloride cotransporter 2 (KCC2) plays a critical role in inhibitory neurotransmission through its ability to maintain low intracellular chloride levels in mature neurons. Surprisingly, KCC2 has also recently been found to interact with proteins involved in excitatory neurotransmission, including the kainate receptor (KAR) subunit GluK2. It is known that the physical interaction between KCC2 and GluK2 is important for KCC2 expression and oligomerization. However, it is unknown whether the activity of KARs can influence KCC2 function. In this study we hypothesized that the activation of KARs would increase KCC2 function. We tested this hypothesis by performing slice electrophysiology experiments in the CA3 region of the hippocampus, recording EGABA as a measure of KCC2 function. We found that activation of KARs with 1uM kainate, which activates both the canonical (ionotropic) and noncanonical (metabotropic) signalling pathways, produced a significant hyperpolarization in EGABA and a dramatic increase in the driving force for Cl- through the GABAA receptor. Activation of KARs with 0.1uM kainate, which has been shown to selectively activate metabotropic signalling of KARs, produced an even larger hyperpolarization of EGABA that persisted after washout. Activation of KARs with 1uM kainate and the addition of the G-protein inhibitor n-ethymaleimide (NEM) to isolate ionotropic KAR signalling also produced a hyperpolarization of EGABA, which returned to baseline after washout. These results suggest that the two KAR signalling pathways exert independent effects on KCC2.

1-B-47 The Influence of Postsynaptic Structures on Missing Quanta at the Drosophilia Neuromuscular Junction

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Synaptic transmission requires both pre- and post-synaptic elements for neural communication. The postsynaptic structure contributes to the effectiveness of synaptic currents to induce voltage changes in postsynaptic cells. At the Drosophila neuromuscular junction (NMJ), the subsynaptic reticulum (SSR) consists of elaborate membrane folds that link the synaptic contacts to the muscle, but its role in synaptic physiology is poorly understood. In this study, I investigate the function of the SSR by conducting electrophysiological experiments on genetic mutants that up- or down regulate SSR complexity. I observed that some synaptic currents do not result in postsynaptic voltage changes, events called “missing quanta”. Furthermore, the frequency of missing quanta is positively correlated with SSR complexity, observed in both naturally occurring variations of the SSR and in genetic mutants. Based on cable theory, I develop an electrical circuit framework to propose that the SSR contributes to the missing quanta by acting as a filter or a switch for some synaptic events. Further studies directed at understanding the role of the SSR in synaptic transmission and the potential for regulating “missing quanta” will yield important information about synaptic transmission at the Drosophila NMJ.

1-B-48 The transcription of Neuroligin-1 is regulated by core clock transcription factors

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Introduction: The postsynaptic adhesion molecule Neuroligin 1 (NLGN1) regulates glutamatergic transmission, some forms of learning and the distribution and intensity of sleep. However, little is known regarding the transcriptional regulation of the Nlgn1 gene. We observed that Nlgn1 is rhythmically expressed across the sleep/wake cycle in the mouse forebrain, suggesting regulation by elements of the circadian system. In addition, the Nlgn1 gene contains a canonical E-box that is bound by the transcription factors CLOCK and BMAL1 as a function of time-of-day. The aim of this study was to verify the contribution of specific clock elements to Nlgn1 expression both in vivo and in vitro. Methods: 1) The expression patterns of Nlgn1 mRNA and NLGN1 protein were examined in the forebrain of adult male ClockΔ19 mutant mice by qPCR and Western Blot analysis, respectively. 2) Luciferase assays were performed in COS-7 cells to assess the transcriptional regulation of Nlgn1 by CLOCK/BMAL1 and their homologs. This was also performed with the addition of GSK3β, as it responds to neuronal activity and negatively regulates CLOCK and BMAL1. Results: 1)ClockΔ19 mice show significant alterations in rhythmic expression of Nlgn1 in the forebrain compared to wild-type mice. A similar tendency was observed for NLGN1 protein. 2) Significant transcriptional activation of Nlgn1 by CLOCK/BMAL1 was observed in vitro, and this was significantly inhibited by GSK3β. Conclusions:These data suggest that circadian regulators are contributing to the sleep/wake-dependent regulation of Nlgn1 expression.

C – Disorders of the Nervous System

1-C-49 Insulin stimulates retinal ganglion cell dendrite regeneration through activation of the mammalian target of rapamycin complex 1 (mTORC1) and complex 2 (mTORC2).

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Purpose: Emerging data indicate that axonal injury triggers rapid alterations in retinal ganglion cell (RGC) dendrites. We recently demonstrated that mTORC1 plays a key role in RGC dendrite stability. The purpose of this study was to determine whether RGC can regenerate their dendrites and whether mTORC1 is sufficient to stimulate dendrite regeneration Methods: Optic nerve axotomy was performed in mice expressing yellow fluorescent protein in RGCs.Insulin, a potent activator of mTORC1 and 2, was administered daily starting when dendrites have already retracted. The following compounds were administered:1) rapamycin, a specific inhibitor of mTORC1;2)siRNA against Rictor, an essential component of mTORC2 activity; 3)KU0063794, an inhibitor of mTORC1/2. RGC dendritic trees were 3D-reconstructed and survival was assessed using RBPMS labeling Results: Our data show that insulin, administered systemically or as eye drops, restored branch length, complexity and field area.Administration of insulin with rapamycin resulted in loss of complexity, while length and field area were preserved. In contrast, combined insulin and siRictor resulted in loss of dendritic length and field area but did not alter complexity. KU0063794 completely abrogated dendrite regeneration. Insulin-mediated RGC survival depended on both mTORC1 and 2. This study demonstrates that insulin promotes RGC dendrite regeneration after axonal injury, with mTORC1 controlling tree complexity and mTORC2 governing dendrite elongation. This may have implications to prevent synaptic loss and visual deficits in glaucoma

1-C-50 Neural synchronizations involved in emotion-detection in psychiatry: Exploration by depth electrodes in bipolar patients

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Neuroimaging studies have revealed that individuals with bipolar disorder (BD) display central nervous system abnormalities. The altered neuronal synchronizations at play are thought to operate on short time scales, detectable only by electrophysiological recordings. This study examined the neuronal network dynamics of two depressive-BD patients with implanted depth electrodes in the ventromedial prefrontal cortex. Modulations of local field potentials and multi-unit activity were investigated when subjects performed an emotion detection-task on a video of morphing faces going from either happy to sad (H-S) or sad to happy (S-H). Time-frequency maps revealed increases in beta- and alpha-band frequencies before and after, respectively, the button press in the H-S condition that were superior to those in the S-H condition. Concurrently-acquired scalp EEG recordings were also explored. Lastly, Microsoft's Oxford Project algorithm for emotion classification was applied to the face stimuli. The objective rating of emotion-change was compared with the patients' answers and both approaches were used to extract power features from the brain signals that were then used to predict patient behavior using machine learning. The findings from this rare intracranial dataset could help elucidate the neural circuitry involved in the negative bias of depressed patients, an important step for the development of future treatment.

1-C-52 Title: The Effects of Childhood Maltreatment on Epigenetic Regulation of the Oxytocinergic System in Male Suicide Completers

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Oxytocin is a mammalian neurohypophysial hormone which acts primarily as a neuromodulator in the CNS. The early development of secure attachments, relationship quality, and the ability to regulate and manage emotions are all instances of psychological resources influenced by the oxytocinergic system. Previous studies have shown that early life adversity might act to disturb this system during critical developmental periods. A body of literature also supports alterations in the oxytocinergic system as a predisposing factor for suicidal behaviour. Our research looks into the expression of genes regulating the oxytocinergic system in the prefrontal cortex of male suicide completers who experienced childhood maltreatment, non-maltreated suicide completers, and healthy controls. Our gene expression data from the prefrontal cortex indicates an effect of abuse on genes involved in oxytocin metabolism and function. Specifically, suicide completers with a history of early life adversity show a significant upregulation of LNPEP (an enzyme responsible for the breakdown of neuropeptides in the brain), OXTR (oxytocin receptor), and AVPR1B (arginine vasopressin receptor 1 B), when compared to non-maltreated suicide completers and healthy controls. Recently, several studies have identified epigenetic mechanisms influencing the oxytocinergic system, with an emphasis on methylation. We are therefore investigating methylation via targeted bisulfite sequencing of CpG rich promoter regions within LNPEP, OXTR, & AVPR1B.

1-C-53 Cell swelling during simulated ischemia in neocortical brain slices

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During the first few minutes of ischemia, neurons swell as they undergo anoxic depolarization (AD). As water transporters linked to ATP fail, neuronal water accumulates and is not passively lost because neurons lack aquaporins. One proposal is that neurons swell because depolarization evokes a large increase in Na influx with Cl- following via SLC26A11, a voltage-gated chloride channel/transporter. Water then osmotically follows these ions. We examined in live brain slices if slice swelling during simulated ischemia (O2/glucose deprivation, OGD) requires SLC26A11-mediated chloride influx. Neuronal and astrocytic swelling during OGD-induced AD is indirectly imaged in live coronal brain slices as a front of elevated light transmittance (LT) moving across the neocortex. We compared swelling and its time course at 34oC during AD in a) regular aCSF; b) low-chloride aCSF (NaCl replaced with Na-isethionate); c) regular aCSF+PPQ-102 or niflumic acid, two drugs that inhibit SLC26A11 function. In low-Cl- aCSF, the propagating AD increased in LT strength and AD onset was not delayed (n=12 slices) compared to control (n=9). Pre-treatment with PPQ-102 at 10-45 uM (n=33) did not delay nor alter AD propagation compared to 27 control slices. Niflumic acid at 100 uM likewise had minimal effect. So in this well-established model of simulated ischemia, SLC26A11-mediated chloride influx apparently plays a minor role in slice swelling. Two-photon microscopy will confirm whether neuronal swelling in particular remains unaffected.

1-C-54 Effects of metformin and enriched rehabilitation on recovery following neonatal hypoxia-ischemia

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Neonatal hypoxia-ischemia (HI) is one of the most common causes of morbidity in children, leaving survivors with profound physical and cognitive disabilities. Effective treatments capable of supporting long-term recovery and reducing the severity of disabilities are needed. Previous research has shown that metformin, an antidiabetic drug, is capable of enhancing motor and cognitive function in various injury models. This study aims to determine whether metformin, enriched rehabilitation (ER) or a combination of the two could provide a clinically relevant option for promoting recovery following HI. Male and female Sprague-Dawley rats were assigned to a sham or HI group. The Rice-Vannucci model was used to induce unilateral injury. At weaning, animals assigned to ER were housed in an enriched environment and received daily reach training for 4 weeks and either metformin or vehicle injections. Motor and cognitive function was assessed using a battery of behavioural tests. Following treatment, HI rats receiving ER took significantly less time to remove tape from their impaired forelimb in the adhesive strip removal task, travelled significantly greater distances in the open field and showed an improved learning curve in the Montoya staircase test compared to those not receiving rehab. In addition, ER rats approached the target location sooner in the probe trial of the Barnes Maze compared to standard housed rats. In conclusion, ER shows promise in promoting recovery of motor and cognitive function following HI, while the effects of metformin are further being investigated.

1-C-55 Advances in Gene Therapy Strategies to Treat Fragile X Syndrome

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Fragile X syndrome (FXS) is a debilitating neurodevelopmental disorder characterized by a loss of scrupulous translational control at the synapse. In FXS, an aberrant CGG trinucleotide expansion upstream of the Fragile X Mental Retardation Protein (FMRP) gene causes drastic downregulation of this translational modulator. The absence of FMRP leads to mental retardation and autistic spectrum-related phenotypes. To correct this disorder we devised an adeno-associated viral (AAV) vector encoding FMRP where its cellular tropism was controlled by the neuron-specific synapsin promoter. Following intracerebroventricular (i.c.v.) injection in neonatal FMRP KO mice, transgene expression, widely distributed through the forebrain, remained stable for over 7 months in terminally differentiated neurons. The FMRP transgene corrected PSD-95 protein hypo-expression in the cortex of Fmr1 KO animals, as well as lowered MeCP2 protein over-expression. Behavioral endophenotypes including hyperactivity, non-social anxiety, pre-pulse inhibition, repetitive stereotypies, and social dominance were fully or partially corrected to WT levels using this viral construct. We then combined i.c.v. injection with additional injections into the parenchyma of more caudal brain regions to achieve wider transduction. This study enables us to determine the proper cellular tropism and the range of FMRP expression required for rescue, as well as the brain regions implicated in FXS neuropathology. These findings are relevant to gene therapy strategies for treating human FXS and other neurodevelopmental disorders.

1-C-56 Inhibition of alpha5GABA-A receptors improves post-traumatic memory deficits

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Introduction: Mild traumatic brain injury (mTBI) accounts for more than 75% of all TBI cases. Deficits in memory and executive function are common and predict poor long-term outcomes after mTBI. The mechanisms underlying these deficits remain elusive and there are no effective treatments. TBI triggers an intense inflammatory response in the brain and previous studies identified α5-subunit containing GABAA receptors (α5GABAARs) as key mediators of inflammation-induced memory deficits. Here, we test the hypothesis that post-traumatic cognitive deficits are caused by increased α5GABAAR activity and that inhibiting α5GABAARs improves cognition after mTBI. Methods: Adult male mice were anesthetized and a free weight drop method was used to produce mTBI. One week after injury, cognitive performance was tested with Novel Object Recognition (NOR), Object Place Recognition (OPR) and puzzle box (PB) assays. To inhibit α5GABAAR, some mice were treated with L-655,708 (L6). Results: Mice exhibited reduced memory performance in NOR and OPR, and impaired executive function, short-term and long-term memory in the PB assay. L6-treated mice showed improved memory performance in NOR and OPR. L6 also improved short-term memory but did not reverse executive function or long-term memory impairment in the PB assay. Conclusions: One week after mTBI, mice exhibited impaired memory and executive function. Inhibiting α5GABAARs reversed the memory impairment but not the executive dysfunction. These results suggest that α5GABAARs are new targets for the treatment of post-traumatic memory deficits.

1-C-57 Sodium nitroprusside reduces psychotic-like behaviour in the ketamine animal model of schizophrenia

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Introduction. Adjunctive sodium nitroprusside (SNP) has been shown in a clinical study to cause rapid long lasting improvement of a number of symptoms in patients with a diagnosis of schizophrenia (Hallak et al., 2013 JAMA Psychiatry).We have now studied the effects of SNP in an animal model (ketamine) of schizophrenia. Methods. Male Wistar rats (250-300g) were divided into 4 groups (Saline+Saline n=4, Saline +Ketamine n=5, SNP+Saline n=5, and SNP+Ketamine n=6) and injected i.p with Saline (0.9% w/v), Ketamine (30mg/kg) and/or SNP (5mg/kg). SNP was administered 30 min prior to Ketamine. Locomotor activity was monitored for 20 min in an open-field square arena. Infrared motion sensors recorded locomotion and non-ambulatory activities (rearing), and the values were averaged in 4 min blocks or as total scores over 20 min. Changes in locomotion patterns in the open field like hyperactivity (increased vertical and horizontal activity) are commonly interpreted as psychotic-like behaviors. Results. Saline+Ketamine rats showed hyperlocomotion at all time points of the open field test when compared to Saline+Saline rats ($p<0.01$). Pre-treatment with SNP prevented Ketamine-induced hyperlocomotion ($p<0.001$). SNP + Saline rats showed no changes in locomotor activity compared to Saline + Saline rats. Conclusion. Pretreatment with SNP can reduce psychotic-like behaviour in an animal model of schizophrenia, and dose-response studies are now warranted. Supported by a Capes/Brazil Scholarship(PAB) and funds from the Universities of Sao Paulo(LK, JEH) and Alberta(GBB).

1-C-58 Theta burst stimulation of the substantia nigra pars reticulata in Parkinson's disease patients

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Parkinson's disease is a debilitating movement disorder characterized by bradykinesia, rigidity and tremor caused by the loss of dopaminergic neurons of the substantia nigra. The loss of dopamine impairs synaptic plasticity in the basal ganglia although levodopa medication restores synaptic long-term potentiation (LTP), induced experimentally by high frequency stimulation (HFS). However, many patients develop disabling dyskinesia with long-term levodopa use. Patterned stimulation, in contrast to continuous HFS, has been shown to successfully induce LTP even in a dopamine-depleted state in the rat model of PD. We hypothesized that theta burst stimulation (TBS: 5 Hz) in the substantia nigra pars reticulata (SNr) and the subthalamic nucleus (STN) will induce LTP in the SNr and compensate for the limited dopamine in OFF state PD patients. Microelectrode recordings of the SNr were obtained during intraoperative mapping procedures in PD patients undergoing deep brain stimulation surgery (DBS). We delivered intermittent theta burst stimulation (iTBS, five 100Hz bursts per second, 100µA, 800 pulses total) and compared the results to patients who received sham stimulation (0µA iTBS) or HFS (continuous, 100 Hz, 100µA, 800 pulses). Our preliminary results show that intermittent theta burst stimulation (iTBS) of the SNr induced LTP in OFF state PD patients whereas sham stimulation or HFS did not induce significant LTP. The results have direct utility to combined levodopa-DBS therapy which can be optimized to target the aberrant synaptic plasticity of parkinsonian basal ganglia.

1-C-59 Pharmacological Chaperones of the Dopamine Transporter Rescue Dopamine Transporter Deficiency Syndrome Mutations

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A number of pathological conditions have been linked to mutations in the dopamine transporter gene, including hereditary Dopamine Transporter Deficiency Syndrome (DTDS). DTDS is a rare condition that is

caused by autosomal recessive loss- of-function mutations in the dopamine transporter (DAT) that often affect transporter trafficking and folding. We sought to identify pharmacological chaperones of the DAT as a potential treatment for DTDS. After screening a set of known DAT ligands for their ability to increase DAT surface expression, we found that bupropion and ibogaine increased DAT surface expression, while others, including cocaine and methylphenidate, had no effect. Ibogaine and bupropion increased wild type DAT protein levels and also promoted maturation of a well-characterized ER-retained mutant K590A, demonstrating an ER- level chaperoning effect. Most importantly, both drugs rescue DAT maturation and functional activity of the DTDS mutations A314V and R445C. Rescue effects are enhanced by HSP90 inhibition, suggesting that ibogaine and bupropion act early on in DAT maturation prior to association with HSP90. Our results show that pharmacological chaperone approaches could be a viable clinical direction for increasing DAT function, particularly in DTDS and other clinical conditions associated with DAT mutations that reduce maturation. To demonstrate that these results are translational, we are currently working on a CRISPR knock-in mouse model of DTDS.

1-C-60 AMP-activated protein kinase, a conserved energy biosensor, signals early neuronal pathogenesis in glaucoma through inhibition of the mammalian target of rapamycin.

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Purpose: The adenosine monophosphate-activated protein kinase (AMPK) is an evolutionarily kinase that plays a crucial role in maintaining energy homeostasis. Active AMPK can then inhibit the downstream mammalian target of rapamycin (mTOR), a key regulator of cell growth and protein synthesis. Here, we asked whether there is metabolic stress in experimental glaucoma and, if so, does it result in AMPK activation, loss of mTOR function and neurodegeneration? Methods: Unilateral elevation of intraocular pressure was induced in mice by injection of magnetic microbeads. AMPK or mTOR activity was assessed by immunohistochemistry. Inhibition of AMPK was achieved by administration of compound C (CC) or by injection of siAMPK. mTORC1 function was inhibited with rapamycin. RGC soma or axons were quantified and RGC dendrites were analyzed in Thy1-YFP mice. Results: Our data demonstrate that OHT triggers rapid upregulation of AMPK activity in RGCs that results in marked loss of mTOR function in these neurons. AMPK inhibition with CC or siRNA effectively restored mTOR activity and promoted robust RGC soma and axon survival. Moreover, recovery of mTOR function resulted in RGCs with longer dendrites and more complex arbors than control retinas. Administration of rapamycin obliterated RGC neuroprotection demonstrating that the response to AMPK modulation was mTORC1-dependent. Conclusions: This study reveals that OHT leads to early metabolic stress in glaucoma which contributes to RGC damage through activation of the energy biosensor AMPK and loss of mTOR signaling in vulnerable neurons.

1-C-61 Microglia are recruited at the interface of infiltrating leukocytes and the astroglial scar after spinal cord injury.

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After spinal cord injury (SCI), monocytes are recruited from the blood into the spinal cord parenchyma, where they differentiate into monocyte-derived macrophages (MDMs). Because MDMs and microglia express similar cell-surface markers, and because microglia acquire a similar morphological phenotype than MDMs upon activation, these cell populations are almost impossible to distinguish from each other

after SCI. Here, we introduce a new mouse model that allows to distinguish microglia from MDMs, resulting from the breeding of three genetically distinct mouse lines: 1) Cx3cr1-creERT2 mice, which express a tamoxifen-inducible Cre recombinase under the control of the Cx3cr1 promoter; 2) Rosa26-TdTomato (TdT) mice, which express a loxP-flanked STOP cassette preventing transcription of a CAG promoter-driven TdT; and 3) LysM-GFP knock-in (ki) mice, which express the GFP reporter in mature granulomyelomonocytic cells. By inflicting a contusion trauma to the spinal cord of this mouse model, we show that microglia at the lesion epicenter degenerate and produce danger signals (DAMPs), within the first 24 hours. From 4 days post-SCI, MDMs infiltrate the lesion core peaking at day 7. Meanwhile, extensive proliferation of microglia in spinal cord parenchyma surrounding the lesion site appears to prevent MDM spreading. Notably, the microglial population peaks at day 14 and forms an interface between MDMs and astrocyte end-feet. These microglia-astrocyte interactions are maintained up to at least day 35, suggesting that microglia regulates astrocytic and macrophage responses to injury.

1-C-62 Brain-derived progenitor cells - potential for therapeutic neurotrophic factor delivery

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Brain biopsies from living Parkinson's disease (PD) patients, taken during deep brain stimulation surgery, can yield large numbers of progenitor cells with key merits of being both host- and brain-derived progeny. Interestingly, these brain-derived progenitor cells (BDPCs) express a broad array of neurotrophic factors (NTFs) that include the most promising and potent cytoprotective agents against PD neurodegeneration. The colocalization of multiple NTFs (e.g., GDNF, BDNF, CDNF) with progenitor and neural proteins raises the intriguing prospect that BDPCs may effectively integrate back into the brain to confer broad and enduring therapeutic function in PD and other neurodegenerative diseases. The present study investigates a population of BDPCs cultured from Fischer rats using Western blot, PCR and immunocytochemistry. We show that rat BDPCs express a similar neurotrophic factor and progenitor marker profile to that of human BDPCs. Further, we assessed short-term in vivo localization and migration of rat BDPCs using MRI. Rat BDPCs were labelled using Molday Ion Rhodamine B©, an iron oxide nanoparticle with a fluorescent tag. These cells were then injected into the striatum of a Fischer rat and were still easily visualized after 1 month. BDPC fluorescence in the striatum was also confirmed immunohistochemically. This study provides novel insight on BDPCs in a syngeneic autologous cell graft model, further supporting therapeutic potential of these cells. These findings help bring us closer to personalized cell-based therapy for Parkinson's and other neurodegenerative diseases.

1-C-63 Modeling the cognitive impairments of schizophrenia: acute amphetamine and PCP are most suited for representing impulsivity, compulsivity, and avolition using 5-CSRTT

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The negative and cognitive symptoms of schizophrenia remain intractable to antipsychotic treatment. One of the approaches used in pre-clinical research to model cognitive symptoms, such as impaired attention, is pharmacological manipulation, such as chronic amphetamine or sub-chronic phencyclidine (PCP) administration. However, the ability of acute treatment with these drugs to produce attentional impairments in animals has not been fully investigated. Therefore, in the present study we used the 5-choice serial reaction time task (5-CSRTT) to test the ability of acute systemic amphetamine (0.5, 1

mg/kg) and PCP (2.5, 3.5, 5 mg/kg) to impair attentional, inhibitory, and/or motivational performance, as well as the ability of antipsychotics and a novel allosteric modulator (PAOPA) of the dopamine D2 receptor to ameliorate impairments. Sprague Dawley rats were trained on 5-CSRTT until they performed under standard parameters consistently, and tested using variable stimulus duration. The results suggested that acute amphetamine and PCP are not suitable models for representing attentional impairments using 5-CSRTT. Instead, they may be more appropriate for modeling other facets of schizophrenia: impulsivity, compulsivity and a lack of motivation. Lurasidone and clozapine, but not olanzapine, offered some but not complete amelioration; PAOPA provided even more modest amelioration, and haloperidol did not alter performance. This study provides researchers investigating cognitive impairments in schizophrenia with some guidance on how to model specific aspects of the illness.

1-C-64 Phase coherence of inhibition with seizure states in a rodent model of neocortical epilepsy

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Synaptic inhibition can modulate the seizure state through the release of GABA onto local targets. In the juvenile mouse hippocampus, it was reported that inhibition predominates in the early ictal phase and fails at ictal onset. Also, in the rodent neocortex, when the inhibitory restraint failed, pyramidal neurons took on the seizure state in local recruited clusters. A further study showed a strong interneuronal spike synchronization during the low voltage fast activity of the tonic phase of the ictus. This study compares the coherence of spontaneous and evoked GABA release with the seizure states. In vitro whole cell patch clamp recordings were taken of layers II and III pyramidal neurons and spontaneous inhibitory currents (sIPSCs) were observed by holding these cells at their reversal potential for excitatory currents. Electrically evoked IPSCs (eIPSCs) from deep layer V onto pyramidal neurons of layer II and III allow a comparison of functional local interneuron to pyramidal cell circuitry during the seizure states. Spontaneous recurrent seizure like events arose when Mg2+ was omitted from the bath solution. The changes of the frequencies of sIPSCs were coherent with the different phases of the seizure states. A similar pattern emerged for eIPSCs. This research demonstrates a participating neuronal population in the cyclical nature of the neocortical seizure-like events.

1-C-65 Quantitative EEG in the Evaluation of Patients with Post-Concussion Syndrome and Chronic Pain Following a Motor Vehicle Accident

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Despite increased awareness, the diagnosis of mild traumatic brain injury (mTBI) remains difficult and controversial. People who develop chronic pain after a motor vehicle accident (MVA) often demonstrate symptoms suggestive of post-concussion syndrome (PCS). Quantitative electroencephalography (qEEG) is a tool that provides objective information about brain function, and may contribute additional information to the clinical diagnosis of PCS. Our objective is to use qEEG to isolate potential electrophysiological biomarkers in our patient population. We conducted a retrospective case-control study using qEEG data from 27 patients with chronic pain and PCS following MVAs, and 27 healthy age- and sex-matched controls. The data was collected and analyzed using 19 electrodes positioned via the standard EEG 10-20 system. Using student unpaired t-tests we measured group differences in phase

locking and absolute power across all EEG channels and all frequency bands. These analyses revealed significant abnormalities in the patient group for both phase locking and absolute power. Unlike many other neuroimaging technologies, qEEG can be obtained at reasonable cost in an outpatient clinical setting which is imperative for reducing financial burden on the healthcare system. The present study provides evidence for the potential clinical usefulness of qEEG. The incremental goal of our research program is to identify biomarkers specific to PCS independent of chronic pain, and vice versa, to help clinically differentiate between these potentially co-morbid conditions.

1-C-66 Blocking spinal P2X7Rs attenuates morphine withdrawal

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Repeated opioid use can lead to physical dependence, which manifests as a withdrawal syndrome upon cessation of drug use. Converging evidence suggests that opioid withdrawal is critically mediated by cellular changes in the spinal dorsal horn. In the present study, we examined the role of spinal ATP-gated P2X7 receptors (P2X7Rs) in morphine withdrawal. Following 5-days of treatment with escalating doses of morphine, rats were injected with the opioid receptor antagonist, naloxone, to rapidly precipitate withdrawal. Morphine treated animals displayed a robust spectrum of withdrawal behaviours characterized by autonomic and somatic hyperactivity. To assess the role of spinal P2X7Rs in morphine withdrawal, we intrathecally injected the selective P2X7R antagonist, A-740003, into morphine dependent animals 1-hour prior to naloxone-precipitated withdrawal. This acute injection significantly attenuated the physical signs of morphine withdrawal. In contrast, continuous delivery of A-740003 into the intrathecal space for the first 72 hours of morphine treatment did not attenuate withdrawal signs. Analysis of spinal cord homogenates from morphine-withdrawn animals revealed a marked increase in spinal P2X7R protein expression. Using flow cytometry, we found that morphine treatment increased P2X7R expression exclusively in the microglial population. Collectively, our findings reveal a critical role for spinal microglial P2X7Rs in the expression of morphine withdrawal.

1-C-68 Age-dependent increase in membrane lipid deregulation observed in brain regions vulnerable to neurodegenerative diseases

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Amyloid load is thought to be an important factor in the development of AD possibly through interactions with other factors that increase the brain's vulnerability to pathology. One possible point of interaction that has been largely ignored is lipid deregulation, specifically, membrane lipids such as gangliosides. Shifts in ganglioside patterns have been observed in a number of brain-related pathologies but have also recently been reported in the natural aging process (Sugiura et al., 2008). The significance of the spatial distribution of these lipid species and whether this phenomenon occurs in other brain regions vulnerable to age-related pathology remains unknown. MALDI Imaging Mass Spectrometry was used to visualize the distribution of A-series ganglioside species across the striatum, ventricles, hippocampus and substantia nigra, as well as to calculate the ratio of expression between different species in young and aged WT and TG APP rats. A trend of increased abundance of c20 ganglioside species was observed in an age-dependent manner in both the WT and TG rats and TG APP rats displayed a trend of increased 20:18 carbon ratio compared to the age-matched WT animals. The shift in the pattern of ganglioside abundance with age and its exacerbated deregulation in the presence of high

levels of amyloid in the brain of TG rats suggests that abnormal ganglioside patterns contribute to brain vulnerability and may play a mechanistic role in the development of neurodegenerative diseases in aging individuals.

1-C-69 An optogenetic kindling model of neocortical epilepsy

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To investigate circuit changes associated with seizures, we developed a novel optogenetic kindling model of epilepsy. We hypothesized that repeated high-frequency stimulation rewires neuronal circuits by recruiting Hebbian plasticity. To test this idea, we expressed Channelrhodopsin-2 bihemispherically in primary motor cortex of male C57BL/6J mice by injecting AAV5-CaMKIIa-hChR2-E123T/T159C-p2A-EYFP. After a 21-day-long recovery period, we bilaterally stimulated awake behaving animals every 48 hours using fiber-coupled 445-nm lasers while recording video and EEG. We could not elicit seizures in early stimulation sessions, but they gradually emerged after ~13 sessions (6 out 6 animals). We found that seizure duration and seizure severity, as well as number of seizures increased with session, while seizure threshold was decreased. We also examined long-term retention of seizure susceptibility by halting stimulation for 36 days and then restarting it. In rekindling sessions, seizures occurred in fewer days and with greater intensity than in control sessions. Finally, we found no gross injury or glial activation in kindled brains. Our results show that repeated brief optogenetic stimulation of otherwise healthy mouse brains can drive them to seizures and that this transition can occur in the absence of brain damage, with animals retaining an elevated seizure susceptibility for weeks. In our model, we obtained more precise control over which neurons were firing and how they fired, which will permit us to explore the role of specific cell populations in epileptogenesis.

1-C-70 The influence of beta-amyloid on intrinsic brain network adaptation in Parkinson's disease

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Objective: There is growing evidence that amyloid deposition contributes to altered functional connectivity (FC) of brain networks in neurodegenerative disease. We aimed to determine whether amyloid levels influence functional connectivity (FC) within and between intrinsic brain networks and cognitive performance. Methods: PD patients (n=24) and healthy elderly controls (n=17) underwent a [11C] PIB PET scan to measure amyloid retention, and a resting state MRI scan to obtain a set of intrinsic brain networks using independent components analysis (ICA). The (DMN), salience network (SAL), left and right executive control networks (LECN & RECN) and the sensorimotor network were selected as networks of interest. Mean cortical [11C] PIB was used to investigate the influence of amyloid on FC, and MoCA scores were to determine the relationship between cognition and FC. Results: PD patients demonstrated increased FC within the DMN (mPFC) and LECN as well as increased FC between the DMN and the LECN compared to healthy controls. PD also demonstrated lower FC between the right insula and DMN, and the right insula and sensorimotor network. Amyloid was positively associated with FC between almost all networks. Amyloid levels were also associated with reduced FC within the DMN and LECN. DMN FC was positively associated with cognitive performance, suggesting a compensatory

response. Conclusions: Our findings demonstrate distinct FC changes in PD, including compensatory increases in FC, as well as increased between network coupling and reduced within network FC associated with amyloid.

1-C-71 On the origins of autism: The Quantitative Threshold Exposure hypothesis

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The Quantitative Threshold Exposure (QTE) hypothesis is a multifactorial threshold model that accounts for the cumulative effects of risk factor exposure in both the causation of autism spectrum disorder (ASD) and its dramatic rise over the past 30 years. The QTE hypothesis proposes that ASD is triggered by the cumulative effects of high level exposure to endogenous and environmental factors that act as antigens to impair normal immune system (IS) and associated central nervous system (CNS) functions during critical developmental stages. The threshold risk factors are identified by the assessment of documented epidemiological factors, including obesity, diabetes, infections, genetic factors and environmental exposure to chemicals such as tetrahydrocannabinol (THC) that may interface critical developmental windows linked to ASD. This model may be useful even when the individual contributions of specific risk factors cannot be quantified, as it proposes that the combined quantitative level of exposure to risk factors for ASD rather than exposure to any one risk factor per se defines threshold occurrence rates.

1-C-72 Heme oxygenase-1 modulates microRNA expression in cultured astroglia: Implications for chronic brain disorders

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Background: Over-expression of heme oxygenase-1 (HO-1) promotes iron deposition, mitochondrial damage and autophagy in astrocytes and enhances the vulnerability of nearby neuronal constituents to oxidative injury. These neuropathological features and aberrant brain microRNA (miRNA) expression patterns have been implicated in the etiopathogeneses of various neurodevelopmental and aging-related neurodegenerative disorders. Objective: To determine whether altered patterns of miRNA expression participate in HMOX1-related neural injury. Methods: miRNA microchip assays were performed on HMOX1- and sham-transfected primary rat astroglia and affected miRNAs were further validated by qPCR. The roles of the heme degradation products, carbon monoxide (CO), iron (Fe) and bilirubin on miRNA expression were assessed and salient mRNA targets of the impacted miRNAs were ascertained. Results: In HMOX1-transfected astrocytes, miR-140*, miR-17, and miR-16 were significantly up-regulated, and miR-297, miR-206, miR-187, miR-181a, miR-138 and miR-29c were down-regulated, compared to sham-transfected controls. CO and Fe were implicated in the HMOX1 effects, whereas bilirubin was inert or counteracted the HMOX1-related changes. mRNA levels of known targets of the down-regulated miRNAs and abnormal in various human brain disorders, were significantly increased in the HMOX-1-transfected astrocytes. Conclusion: In chronic CNS disorders, altered expression of salient miRNAs and their mRNA targets may contribute to the neural damage accruing from the over-exprexpression of glial HO-1.

1-C-73 Innate deficits in dendritic outgrowth in Parkinson's patient-derived neurons are rescued by NRF2-mediate activation of the anti-oxidant response

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Parkinson's Disease (PD) is associated with pathological deposits of aggregated α-synuclein (α-syn) in multiple brain regions. While motor dysfunction is a primary phenotype, many patients suffer from cognitive impairment including dementia. PD dementia is highly associated with pathological deposits of aggregated α-syn in neurites. Much evidence suggests that increased Reactive Oxygen/Nitrogen Species (ROS/RNS), resulting from impaired mitochondrial function, contribute to this pathology. However, the mechanism of neuronal loss in PD remains unclear. We utilized a patient-derived hiPSC model of PD that allows for comparison of A53T α-syn mutant neurons against isogenic corrected controls, in addition to a hESC model with the A53T α-syn mutation introduced. Following differentiation to dopaminergic (DA) neurons, we determined that A53T DA neurons display reduced neurite outgrowth and diminished neuritic complexity. Strikingly, neuritic morphology of A53T DA neurons was rescued by treatment with L-NAME, a nitric oxide synthase inhibitor, suggesting a causal link to nitrosative stress. Furthermore, we show that activation of NRF2, a master regulator of the antioxidant response, normalizes neurite outgrowth. Our results reveal innate differences in neuritic morphology between PD-A53T DA neurons and isogenic controls. More importantly, we show that this phenotype can be rescued through the alleviation of nitrosative stress. As such, detoxifying neurons of ROS/RNS through forced activation of NRF2 may provide a new therapeutic avenue against PD and associated dementia.

1-C-74 Intra-VTA leptin decreases the augmentation of heroin seeking induced by chronic food restriction.

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Caloric restriction increases the risk of relapse in abstinent drug users. In an animal model of relapse, chronic food restriction augments heroin seeking during withdrawal. Leptin, a hormone involved in the regulation of energy balance and food intake, attenuates acute food-deprivation induced reinstatement of heroin seeking. However, food deprivation and chronic food restriction result in different metabolic consequences and neural adaptations. Therefore, we investigated the impact of leptin on heroin seeking in chronically food restricted rats. Rats self-administered heroin for 10 days. Rats were then moved to the animal colony for 14 days, and food restricted to 90% of their original body weight or given free access to food. In experiment 1, rats were given one injection of leptin (0.0, 2.0, or 4.0µg; i.c.v.) 24 hours before the heroin-seeking test and a second injection immediately prior to the test. Central administration of leptin did not affect the augmentation of heroin seeking induced by chronic food restriction. Dopamine neurons in the ventral tegmental area (VTA) express high density of leptin receptors, suggesting a direct effect on reward and motivation. Hence, in experiment 2, leptin was administered directly into the VTA (0.00, 0.125, or 0.250µg) prior to the heroin-seeking test. Intra-VTA leptin administration dose-dependently decreased heroin seeking in only the food restricted rats. We conclude that leptin transmission in the VTA modulates the augmentation of heroin seeking induced by chronic food restriction.

1-C-75 A new perspective for the treatment of schizophrenia: positive allostery of the dopamine D2 receptor

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We have investigated the use of a positive dopamine D2 receptor allosteric modulator, PAOPA, in regulating receptor expression as a new approach to treating schizophrenia. In contrast to current forms of antipsychotic medication, which antagonize dopamine binding, PAOPA enhances binding to the dopamine D2 receptor. Our previous studies suggest that positive allosteric modulation with PAOPA leads to subsequent receptor internalization of the dopamine D2 receptor, ultimately decreasing dopaminergic neurotransmission and regulating aberrant receptor expression. In the present study, PAOPA was tested for its therapeutic efficacy across a battery of tests (hyperlocomotion, social withdrawal, sensorimotor gating, novel object recognition, brain metabolic activity, 5-choice serial reaction time task) in the phencyclidine and amphetamine induced rat models of schizophrenia. PAOPA showed therapeutic efficacy in behavioural paradigms representing the positive, negative, and cognitive symptoms of schizophrenia. Interestingly, some behavioural indices that were ameliorated in the amphetamine model were not ameliorated in the PCP model, suggesting that the deficits induced by amphetamine and PCP--while behaviourally and phenotypically similar--are mechanistically different and that PAOPA's effects are limited to certain neural pathways. These studies provide insight into the use of positive allostery for the safe and effective treatment of schizophrenia.

1-C-76 Hippocampal subfield volume loss in children and adolescent survivors of pediatric brain tumors

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Cranial radiation (CR), a neurotoxic brain cancer treatment, is associated with long-term hippocampal volume loss and impaired declarative memory in pediatric brain tumor survivors (PBTS). Studies with adult rodents show differential vulnerability of hippocampal subfields to CR and altered neurogenesis in the hippocampal dentate gyrus (DG). Little is known about the long-term impact of CR on the volume of hippocampal subfields in humans. Hippocampal subfields mediate distinct forms of memory processing, making them an important target in elucidating CRT-induced memory decline. We examined the long-term impact of CR on hippocampal subfield volumes by comparing PBTS (n=17) to healthy controls (n=20). We also assessed the impact of hydrocephalus, a common complication in PBTS in a subset of patients with this condition (n=12). Using an automated segmentation algorithm, we segmented the hippocampus into CA1, CA2/3, CA4/DG, SR/SL/SM and subiculum. We found smaller right CA2/3, left subiculum and marginally smaller left CA4/DG in PBTS compared to controls. Patients with hydrocephalus had smaller left CA4/DG and marginally smaller left hippocampi compared to controls. Our data suggest that hippocampal subfields in the developing brain display differential vulnerabilities to the neurotoxic effects of CR and to injury sustained from hydrocephalus. Volume loss may reflect reduced neuron size, numbers or connections within and between regions. Future work will assess relations between CR dose, hippocampal subfield volumes and memory deficits in PBTS.

1-C-77 Eye movement 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. Some Parkinson's Disease (PD) patients show impaired visual function related to a selection of eye movements but show heightened reflexive eye movements. However, why the loss of DA neurons leads to these deficits in eye movements is not clear. In this study we used the optokinetic response (OKR) of larval zebrafish to explore eye movement deficits in detail. Variables that were tested included amplitude, velocity and number of saccades in eye movements. To generate a PD model of zebrafish in which DA neurons are lost, dat:CFR-NTR transgenic fish were raised in a metronidazole (MTZ) infused environment. MTZ is converted by NTR into a cytotoxic product, and our previous work has shown that it leads to the selective loss of DA neurons. The OKR was tested on groups with ablated dopaminergic neurons and an untreated group. With this method, we found that there are significant differences in several parameters of saccadic eye movements between the treated and untreated animals. This work suggests that zebrafish can be used to study how the loss of DA affects eye movements in Parkinson's Disease.

1-C-78 Effects of an Acute Bout of Soccer Heading on Neurovascular Coupling

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Sport-related head trauma is an important public health issue in Canada. There is a growing evidence base supporting a link between repetitive sub-concussive impacts (such as soccer heading) and cognitive impairments. (1) Adequate cerebral blood flow (CBF) in response to increases in cortical activity (termed neurovascular coupling) is essential for cognitive function. However, very little is currently known about how the neurovascular coupling (NVC) response is altered following repetitive subconcussive events. In this preliminary soccer heading study (n=4), the NVC task consisted of 8 cycles of closing (20 sec) and then opening (40 sec) the eyes to complete a complex visual scene search (Where's Waldo). This task was performed before and after an acute bout of soccer heading (total 40 headers in 20 minutes, average ball speed 74.8 km/hr ± 2.25km/hr). CBF velocity was measured in the posterior cerebral artery (PCAv) via transcranial Doppler ultrasound. Early results demonstrated a slight reduction in baseline PCAv post heading for all subjects (-1.84cm/s ± 2.06) with no change in absolute (pre: 7.34±1.60 cm/s; post: 7.70±1.76 cm/s) or relative (pre: 22.13 ±2.42 %; post: 24.51± 4.67%) peak PCAv increase upon eyes opening. These early preliminary findings indicate that there may be a slight decrease in CBFv, while the NVC response remains intact following an acute bout of soccer heading. 1. Zhang et. al., 2013. Plos One.

1-C-79 IVIg immunotherapy combined with MRI-guided focused ultrasound enhances neuronal plasticity in an amyloidosis mouse model

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the accumulation of amyloid beta peptides (Aβ), neuronal death and cognitive decline. Natural antibodies present in intravenous immunoglobulins (IVIg), collected from healthy blood donors, have been used to treat pathologies present in murine models of AD. Phase III IVIg clinical trials, however, failed to improve cognition in AD patients. This limited efficacy of IVIg could be attributed to the restricted ability of antibodies to get through the blood-brain barrier (BBB). We propose the use of transcranial focused ultrasound (FUS),

guided by magnetic resonance imaging (MRI), to increase BBB permeability temporarily and increase IVIg entry into areas most affected by Aβ pathology. In a mouse model of amyloidosis, IVIg was given intravenously, with or without the application of FUS. After treatment, immunohistochemistry was used post-mortem to evaluate neurogenesis, amyloid pathology and neuronal activation. Our results show that compared to animals treated with saline alone, FUS and IVIg treated animals had significantly reduced Aβ pathology ($p<0.05$) and increased neurogenesis ($p<0.05$). Additionally, neuronal plasticity was significantly increased in the FUS+IVIg treated animals compared to the saline treated controls ($p<0.05$). These findings demonstrate that IVIg drug delivery to the brain by FUS enhances the beneficial effects of IVIg therapies related to Alzheimer's disease.

1-C-80 The role of RGMa/Neogenin Signalling in Multiple Sclerosis

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Multiple Sclerosis (MS) is an inflammatory disease affecting the Central Nervous System (CNS), resulting in a wide range of symptoms including demyelination, glial scar formation and axonal loss. Recently, Repulsive Guidance Molecule a (RGMa) has been implicated in playing a role in T-cell modulation as well as TH17 cell mediated Neurodegeneration as observed in an animal model of MS, Experimental Autoimmune Encephalomyelitis (EAE). Our lab has shown that RGMa exerts its affect through an interaction between its N-terminal domain and the Immunoglobulin domain of Neogenin (4Ig), a receptor for RGMa. We have Preliminary data showing that injection of recombinant 4Ig peptide in EAE mice, thereby blocking N-RGMa/4Ig interaction, ameliorates the clinical severity of EAE compared to control treated mice. We therefore hypothesize that RGMa/Neogenin signaling is critical in the development of EAE. Through computer modeling, we have identified amino acids that may be critical for NRGMa-4Ig interaction. Thus, a series of mutagenesis experiments have been performed on both N-RGMa and 4Ig constructs generating mutant constructs. These mutated constructs contain single amino acid point mutations which will then be used to identify the key amino acids involved in N-RGMa/4Ig interaction through a series of binding assays. Once the key amino acids are determined, this can be used to develop a small molecular drug which will tested in an EAE model. Thus, the RGMa/Neogenin pathway may play a role in MS Development and could be an attractive target for the development of therapies for MS.

1-C-81 Significantly increased total brain volume and other neuroanatomical differences in a mouse model of Nance Horan Syndrome (NHS).

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Introduction Nance-Horan Syndrome (NHS) presents with mental retardation and has been associated with autism. NHS also presents with facial, dental, and ocular abnormalities. NHS has been linked to several genes, including the NHS gene. The purpose of this study was to examine the neuroanatomical differences in a mouse model of NHS with a frame-shift indel mutation in the Nhs gene. Methods 48 fixed mouse brains were examined; 15 Nhs nulls and 33 WT (C57BL6/NCrl). The mice were ~60 days old. MRI Acquisition - A 7T MRI scanner was used to acquire images of the brain with a T2-weighted, 3D FSE sequence, 40 µm isotropic voxels in ~14 h (Lerch et al., 2011). Data Analysis - To visualize and compare any differences the images are registered together to model how the deformation fields relate to

genotype (Lerch et al., 2008). Volume differences are calculated either in voxels or 159 different regions (Dorr et al. 2008, Ullmann et al. 2013, Steadman et al. 2012). Results and Discussion A surprising difference between Nhs null mice and WT was a 10% increase in brain volume ($p<0.01$, FDR<1%). This is one of the larger increases in overall brain volume found in autism related mouse models (Ellegood et al. 2015). The differences stem from the subcortical structures, the cortex was increased in size in several areas, but it was not increased to the same degree as the subcortical structures and cerebellum (Figure 1). This is contrary to what has been seen in other autism mouse models where the cortex is often one of the most affected regions (Ellegood et al. 2015).

1-C-82 Hypoxia resulting from repeated seizures augments memory impairment and AD-like pathology in the 5XFAD mouse.

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Senile plaques have been detected in resected epileptic tissue. Furthermore, amyloid-β (Aβ) is transiently increased following electroconvulsive seizures in people treated for depression. These data support a role for seizures in pathological aggregation of Aβ in epilepsy, but the underlying mechanism of this effect has yet to be identified. Our lab revealed that severe hypoxia occurs after seizure termination and may last over an hour. Given that stroke increases the risk of Alzheimer Disease (AD) and that periods of hypoxia potently up-regulate Aβ, we hypothesized that the hypoxia resulting from seizures, but not the seizures themselves, would accelerate the deposition of Aβ and contribute to memory deficits in a mouse model of AD (5XFAD mice) containing transgenes for 5 different human familial AD mutations. We have previously determined that post-seizure hypoxia is COX-2 dependent and can be prevented with acetaminophen. Mice received 60Hz kindling stimulation to elicit 21 hippocampal seizures between the ages of P30 and P60 in the presence or absence of hypoxia (vehicle vs. acetaminophen). Seizure duration and severity (Racine scale) did not differ between vehicle- and acetaminophen-treated mice, however hippocampal hypoxia and memory impairments were prevented with acetaminophen. We are currently assessing amyloid deposition using spectrally-active amyloid probes (e.g., X-34), and based on preliminary evidence it would appear that hypoxia resulting from repeated seizures not only augments memory impairment, but also AD-like pathology in the 5XFAD mouse model.

1-C-83 Muscarinic acetylcholine receptor type-1 antagonists modulate post-translational modifications of Ca2+/calmodulin-dependent protein kinase kinase beta in adult sensory neurons

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Muscarinic acetylcholine (ACh) type-1 receptors (M1R) mediate metabotropic actions of ACh. Lesions in the central ACh-mediated system are now considered to be a major factor in cognitive and neurodegenerative disorders. Previously we have shown that pirenzepine (PZ) and muscarinic toxin-7 (MT7), selective antagonists of M1R, can induce neurite outgrowth in cultured adult sensory neurons. However, the exact mechanism of their effect on neurite outgrowth is unknown. M1R activation can regulate many signaling pathways and one of the best known is its influence on intracellular Ca2+. Previously, we have shown that M1R antagonism can raise AMPK phosphorylation and resulted in increased mitochondrial activity. Ca2+/calmodulin-dependent protein kinase kinase β (CaMKKβ) is a potential target of muscarinic antagonism as an upstream activator of AMPK and it is strongly expressed

in peripheral neurons. Therefore, in the present study, we used iso-electric focusing to identify the post-translational modification (PTM) of CaMKKβ upon muscarinic antagonist treatment in adult sensory neurons and cells over-expressing M1R-GFP. Our results indicate that CaMKKβ undergoes significant PTMs upon MT7 or PZ treatment, however, the extent and nature of the modifications differed. In adult sensory neurons, CaMKKβ was found significantly relocated from the perikarya to neurites within 1hr of treatment with PZ/MT7. In addition, MT7/PZ treatment significantly altered the association of CaMKKβ with several multiprotein complexes which may be due to the differential PTMs. Funded by CIHR # MOP-130282

1-C-84 Age-Related Changes in Learning and Memory in the Hebb-Williams Maze in the 3xTG Mouse Model of Alzheimer's Disease

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The 3xTG mouse model of Alzheimer's disease develops intracellular plaques at 3 months, extracellular plaques at 6 months, and tau tangles by 12 months of age. We have shown impairments in spatial learning and working memory in 3xTG mice at six months of age (Stevens & Brown, 2015, Behav Brain Res, 496-505; Stover et al., 2015, Behav Brain Res, 29-38), but there was no age-related progression of deficits in these tasks. In the current study, we used the Hebb-Williams maze with food reward to assess learning and memory in 3xTG mice and their B6129SF2 wild type controls at 4 and 7 months of age. In the acquisition (Long-Term Memory) phase, 3xTG mice reached the learning criterion significantly faster than the WT mice and males reached criterion faster than the females. In the test phase (Working memory), 3xTG mice had significantly longer latencies in the hard mazes than the easy and medium mazes, but there was no such difficulty effects for the WT mice. The 4 month old male WT mice had significantly shorter latencies then female WT mice but there was no sex difference for the 3xTG mice. At 7 months of age male and female mice of both genotypes had longer latencies in the hard mazes. Our results show that (1) 3xTG and male mice have better long term memory compared to the WT and female mice. (2) Working memory deficits in the 3xTG mice start as early as 4 months but they can be detected only in difficult tasks. (3) Anxiety and motivation may be affecting the cognitive performance of 3xTG mice and WT controls.

1-C-85 The effect of obesity on the vascular and glial response to endothelin-1 induced focal ischemic stroke.

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Obesity is a high risk factor associated with ischemic stroke and results in poorer neurological outcomes post-stroke. Diet-induced obesity in rodents results in larger infarct volumes and worse behavioural deficits compared to chow fed controls following ischemic stroke. The chronic inflammation associated with obesity may cause neurons, glia and endothelial cells in the ischemic brain to become more vulnerable to insult. To address this, we are examining the effect of obesity on the vascular and glial response to a focal ischemic stroke. Three week old male C57BL/6 mice were fed a high fat diet for approximately 3 months prior to stroke. Intracortical injections of the vasoactive peptide Endothelin-1 (ET-1) were used to induce a focal ischemic stroke. Tissue was collected 7 days post-stroke for histological and immunohistochemical analysis. Mice fed a high fat diet weighed significantly more than chow fed mice. An increase in microglial/macrophage activation was seen surrounding the infarct region

in obese mice at 7 days post-stroke. In contrast, the astroglial response encompassing the ischemic area was similar in obese and control mice. Our results demonstrate that obesity amplifies the immune response to a focal ischemic stroke. Future studies are focussed on examining the effect of obesity on vascular reperfusion and the cellular response in the acute stage (up to 48 hrs) post-stroke. Understanding the impact of obesity on the ischemic brain is essential for future therapeutic interventions and improving post-stroke recovery.

1-C-86 Repeated Seizures Alter the Functional Integration of Adult-Born Neurons into Behavioral Circuits

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Adult neurogenesis is a developmental process encompassing the birth of new neurons and their integration into the existing neuronal circuitry. As new neurons begin the process of integration, they pass through a transient period of heightened plasticity. This critical period lasts ~2 weeks in rats, and it is during this time that newborn cells are more highly excitable than their mature counterparts. The critical period permits new neurons to be readily modified and impacted by experience enabling them to play a key role in supporting hippocampal functions such as spatial learning and memory. In this study, we employed PTZ kindling to examine the impact of repeated seizure stimulation on neurogenesis and circuit integration. First, subjects were treated for 5 days with the proliferation marker BrdU, and then underwent 1- or 2-weeks of PTZ kindling. Twenty-four hours after kindling, subjects were exposed to a novel contextual environment to examine the integration of new neurons into networks that mediate spatial information processing. We found that PTZ kindling reduced the activation of new neurons (as inferred by examining expression of IEG products) following exposure to novel environment. These findings suggest that recurrent seizures disrupt the critical period of circuit integration of newborn neurons into behavioral circuits providing a possible explanation for the presence of impaired spatial learning and memory in individuals with chronic epilepsy. Studies are underway to examine the mechanism(s) that may account for reduced integration of newborn neurons.

1-C-87 Microelectrode Recordings of the Internal Segment of the Globus Pallidus in Cerebral Palsy

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Cerebral palsy (CP) encompasses a range of conditions involving motor and postural dysfunction, resulting from damage to the developing central nervous system. Individuals with cerebral palsy often develop secondary dystonic symptoms, for which deep brain stimulation (DBS) of the internal Globus Pallidus (GPi) can be indicated. However, DBS of the GPi in patients with secondary dystonia has had mixed outcomes. Conversely, DBS of the GPi in individuals with primary dystonia has been proven to be an effective long-term treatment. To investigate this further, we took microelectrode recordings (MER) prior to the implantation of bilateral GPi-DBS electrodes to measure the firing rates and patterns of GPi single-units in five CP patients. Moreover, we were able to examine the effects of general anesthesia (GA) on the firing properties of CP Gpi cells in relation to dystonic symptoms. We found that the firing rate of CP GPi units under GA to be lower (mean ± standard deviation; 24.5 ± 11.7 Hz; n=44) than CP GPi units that were not under GA (52.4 ± 6.5 Hz; n=3; $P<0.01$). CP GPi cells under general anesthesia also had a proclivity for a higher median burst index value (2.3 ± 1.9) compared to non-anesthetized CP GPi cells

(1.2 ± 0.2; P=0.19). Furthermore, 28.3% of CP GPi cells were characterized by an irregular bursty firing pattern, compared to 0% of non-anesthetized cells. Our preliminary results suggest that GA is responsible for the lower firing rate of GPi neurons, and hence the lower firing rate is not responsible for the dystonic symptoms of CP.

1-C-88 Role of altered palmitoylation in mis-trafficking of NMDA receptors in Huntington disease mouse model

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N-methyl-D-aspartate receptors (NMDAR) play a critical role in excitatory synaptic signaling, and synaptic/extrasynaptic NMDAR balance impacts neuronal survival. We found enhanced extrasynaptic GluN2B-type NMDAR activity in striatal neurons in the YAC128 mouse model of Huntington disease (HD), resulting in a shift toward cell death signaling that contributes to striatal vulnerability. Huntingtin (Htt) protein interacts with palmitoyl acyltransferases DHHC17 and DHHC13, aka huntingtin-interacting protein-14 (HIP14) and HIP14-like (HIP14L), and palmitoylation of certain synaptic proteins is reduced in YAC128 mice. Notably, GluN2B palmitoylation on two cysteine clusters regulates its trafficking to surface membrane and synapses in cortical neurons. Here, we investigated whether altered GluN2B palmitoylation contributes to its accumulation at extrasynaptic sites in striatal neurons from YAC128 mice. We found reduced GluN2B palmitoylation in YAC128 striatum. Moreover, NMDAR containing cluster II (but not cluster I) palmitoylation-resistant mutant GluN2B (GluN2B 5CS) showed enhanced surface expression in striatal neurons in wild-type corticostriatal co-cultures, mimicking the effect observed in YAC128 co-cultures. Importantly, increased striatal surface GluN2B 5CS was restricted to extrasynaptic membranes. These data suggest that reduced GluN2B cluster II palmitoylation contributes to mutant Htt-induced alterations in NMDAR trafficking. Experiments are ongoing to investigate potential roles for HIP14 and HIP14L in altered GluN2B-NMDAR trafficking in YAC128 striatum.

1-C-89 Detecting covert levels of awareness using a hierarchy of cognitive and different neuroimaging modalities in patients with disorders of consciousness.

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Several reports have examined different aspects of cognitive function preserved in patients with disorders of consciousness (DOC) showing that multiple tasks and modalities provide the best opportunity for a patient to demonstrate covert awareness. With a wide range of aetiologies and comorbidities, this is a very diverse population with variable cognitive and behavioural abilities. Additional challenges are the availability of specific technology as well as the eligibility of individual patients to be assessed with functional Magnetic Resonance Imaging (fMRI) or Electroencephalography (EEG). Our objective was to use different modalities and tasks with a hierarchical approach to assess covert levels of awareness in DOC patients. 20 patients with severe brain injury and DOC diagnoses ranging from Vegetative State (VS) to EMCS (Emergence from Minimally Conscious State) participated in EEG and fMRI assessments. 11 additional patients were only eligible to participate in EEG studies. We used a variety of stimuli including questions, active tasks, and passive stimuli. All 31 patients were evaluated using the Coma Recovery Scale - Revised (CRS-R). We were able to assess a range of cognitive

functions that covered basic auditory, visual, and tactile processing and then exploring speech specific processes, selective attention, executive function, and command following. This allowed us to establish the depth and breadth of preserved cognitive function in these patients that went from basic auditory processing all the way to sophisticated command following covering a wide spectrum.

1-C-90 Behavior as a signature of neuroimmunological interactions

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Sickness behavior has long been considered similar across many diseases as being an adaptive response that conserves energy for the benefit of the organism. Recent data suggest that these changes may contribute to a vicious circle of amplification of inflammation driving behaviors that are associated with increased inflammatory status. The goal of this study is to dissect differences in mouse behavior during multiple sclerosis (MS), a demyelinating and neurodegenerative disease, which is one of the leading causes of disability of young people. We hypothesized that in addition to motor disturbances, multiple types behaviors will be affected. We used C57Bl6 mouse model of MS, experimental autoimmune (EAE), and multivariate clinical assessment system to follow mice 24 hours a day for 4 weeks and 8 weeks. We found dramatic differences in multiple behaviors between healthy, OVA immunized (control) and EAE animals. EAE mice had a 3 fold decrease in chewing behavior, while OVA immunized (control mice) remained similar to healthy mice. OVA immunized mice's amount of time spent eating has increased, while mice with EAE demonstrated a 3 fold decrease. Grooming behavior increased only in mice with EAE. Sniffing behavior decreased two fold for OVA immunized mice while increased two fold in mice with EAE. The multivariate clinical assessment aproach is fully computerized and is not subject to human bias. We believe that this novel method analyze animal behavior will help to understand how different phases of diseases are correlated to different behaviors and biochemical mechanisms.

1-C-91 Tardive dyskinesia induced by prolonged antipsychotic treatments in a non-human primate model is associated with Akt/GSK-3Beta kinase activities

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Tardive dyskinesia (TD) is a delayed and potentially irreversible motor complication arising after chronic exposure to dopamine receptor antagonists. Typical antipsychotic drugs, metoclopramide and several atypical drugs are associated with the development of TD. But, the pathophysiology of TD remains elusive. Antipsychotics modulate multiple kinase pathways, but their involvement in TD is unknown. To investigate the neurochemical basis of TD, we exposed capuchin monkeys to prolonged haloperidol (N=11) or clozapine (N=6) treatments. Six untreated animals were used as controls. Five haloperidol-treated animals developed mild TD similar to that found in humans. No TD was observed in the clozapine group. We measured ERK1/2, GSK-3β and Akt activities with phospho[Thr202/Tyr204]-p44/42 (pERK1/2), phospho[Ser9]-GSK-3β (pGSK-3β) and phospho[Ser473]-Akt (pAkt) specific antibodies by Western blots. Haloperidol, but not clozapine, strongly enhanced pERK1/2 immunoreactivity in the putamen. Nonetheless, no difference was observed in the incidence of TD. In contrast, haloperidol reduced putamen pAkt and pGSK-3β immunoreactivity. Interestingly, only haloperidol-treated monkeys that did not develop dyskinesia have reduced pAkt and increased pGSK-3β levels, as compared to dyskinetic animals, and pAkt levels nicely correlated with dyskinetic scores ($r2 = 0.72$; $p<0.05$). Elisa assays will be used to complete the molecular cascade and detect changes in β-arrestin2 and GRK6

protein levels. Our results suggest that changes in Akt and GSK-3β activity are correlated with the severity of TD.

1-C-92 The effect of Dopaminergic therapy on Stimulus-response learning and decision-making in Parkinson's disease using 3T MRI

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Dorsal striatum (DS) function is impaired whereas ventral striatum (VS) processes are relatively spared in Parkinson's disease (PD). These brain regions are also differentially affected by dopaminergic (DA) medication in PD. DS function is remediated by DA therapy, whereas VS processes are impaired by DA therapy presumably due to DA overdose. Our aim was to determine the neural correlates of stimulus-response (SR) learning in PD patients on and off DA therapy using fMRI, using a task shown previously to engage both DS and VS. 16 PD and 15 healthy controls completed an SR learning task during which they learned to associate abstract images with a button-press response via feedback. Feedback was provided after each response, facilitating learning through trial and error. Patients with PD completed the task twice on consecutive days, once ON and once OFF DA medication. Data from the healthy elderly controls replicated our previous findings with healthy young controls. DS activation correlated with SR decision-making events, and VS was recruited when learning through feedback occurred, suggesting that VS mediates learning whereas DS underlies decision-making processes. Learning slope was steeper, suggesting more efficient SR learning for PD patients off relative to on DA therapy, though greater DS activation occurred at the time of decision making for PD patients on compared to off DA therapy. VS activation, at the time of feedback, was depressed in PD patients compared to controls. These results suggest that overdose of VS, is a mechanism for cognitive dysfunction in PD.

1-C-93 Prevalence of incidental findings in a multi-diagnosis psychosis, addiction and infection population in Vancouver's Downtown Eastside

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The Hotel Study is a longitudinal epidemiological investigation of socially disadvantaged Downtown Eastside residents and includes psychiatric, psycho-social and biomedical assessments. The Downtown Eastside neighbourhood of Vancouver has the largest open-air illicit drug market in North America and the largest rate of homelessness in the city. Neuroimaging studies have shown abnormalities that show long-term drug use may lead to physiological changes and neural damage associated with cognitive impairment. As part of this study, high-resolution brain magnetic resonance imaging was obtained yearly and images were reviewed by a neuroradiologist. While incidental findings are relatively common in the general population (5-20%), preliminary analysis indicated that this population has a significantly elevated rate of total numbers of incidental findings (>80), including cerebrovascular abnormalities (e.g. aneurysms, hemorrhages and infarcts), traumatic brain injuries and parenchymal volume loss greater than expected for age. Both life history and chronic illicit substance use are thought to contribute to these phenomena. We predict adverse effects on cognition would be seen in individuals with a greater burden of neurological damage. The co-morbidity of neuropathologies parallels the co-morbidity of

general health issues. Better understanding of these neuropathologies may provide evidence of new approaches to treatment strategies.

1-C-94 ERP abnormality induced by cholinergic deficiency in rats: a potential biomarker for Alzheimer's disease

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A pathological feature in Alzheimer's disease (AD) is the progressive loss of cholinergic neurons. Past studies showed that the loss of cholinergic neurons precedes detectable memory decline by many years (Beach et al., 1997). This raises a need for a method, other than memory tests, to detect early pathology in the brain. The present study examined whether event-related potentials (ERPs) can be used for this purpose. Adult rats were injected subcutaneously either with muscarinic acetylcholine receptor antagonist, scopolamine (0.05 mg/kg; scop group) or saline (saline group) before they received pairings of a stimulus (CS+) with eyelid shock (US) in parallel to the presentation of another stimulus alone (CS-). During this period, electroencephalogram was obtained with screw electrodes placed on the skull over the frontal, parietal, and temporal cortices. We found that compared against the saline group, the scop group required more sessions to acquire the conditioned responses (CR) to CS+ while inhibiting CR expression to CS-. In parallel, in the saline group, the amplitudes of frontal P1 and parietal N1 ERP components were significantly larger in response to CS+ than CS-; however, these differential responses were not observed in the scop group. Moreover, the amplitude of the parietal P1 component was significantly reduced in the scop group regardless of CS+ or CS-. Thus, the amplitude of frontal P1, parietal P1, and N1 components are sensitive for central cholinergic deficits similar to a pathological feature observed in AD brains.

1-C-95 A three-dimensional map of hindlimb movements evoked by intraspinal microstimulation in the lumbar spinal cord in rats

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A 3D map of motor outputs from the lumbar spinal cord to hindlimb skeletal muscles was derived using intraspinal microstimulation (ISMS) in healthy, adult, male, Sprague Dawley rat. Under ketamine/xylazine anesthesia, fine wire electromyographic (EMG) electrodes were implanted into 4 muscles of both hindlimbs. After T13-L1 laminectomy and removal of the dura, a four-shank microelectrode array (NeuroNexus) was implanted into the spinal cord at the lumbar level corresponding to a 3D grid. Shanks were 200 µm apart, and each shank had four 40 µm diameter sites (impedance ~30-40 kΩ). Stimulation sites were located ~140-2200 µm below the dorsal surface of the cord, from ~400-800 µm lateral to the midline on both sides of the spinal cord, and from ~0.6-10 mm from the caudal end of the T12 vertebra. Biphasic pulse trains, each consisting of 3 pulses, (200 µs duration; 300 Hz) were delivered at 1 sec intervals to define EMG and movement thresholds (avg. range = 2-20 µA). Stimulus-Triggered Averaging (StTA) of rectified EMG responses was used to determine response latency. Hip movements predominated in rostral T13, while medial leg rotation was more common in caudal T13. In L1, ankle, digit and medial leg rotations were elicited. Further caudally in L1, knee movements were typically evoked in both hindlimbs. StTAs of EMG activity revealed a latency of ~4 ms. The derived motor map provides important data for guidance of intraspinal probes for neuroprosthetic devices currently in development.

D – Sensory and Motor Systems

1-D-96 Relative contributions of perception and prediction to hand localization in visuomotor adaptation

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Motor learning should change predictions about the sensory outcome of actions, and hence affect state estimates of limb position. Several studies have used localization of the invisible, trained hand with their visible untrained hand to assess changes in predicted sensory consequences of actions after motor learning (Izawa & Shadmehr, 2012; Synofzik et al., 2008). However, since our lab has shown that motor learning also changes proprioception of the hand, the question remains how much proprioception and prediction contribute to changes in hand localization. We quantified this by having 21 participants localize their hand after training with aligned visual feedback and with a gradually introduced visuomotor rotation of 30°. Before each localization there was a hand movement. Crucially, this movement could be actively generated by the participant, so that an efference copy allows predictions, or it could be passive, controlled by a robot. Both reflect changes in perceived hand position, so that the relative contributions to hand localization can be determined. We found a significant change in hand localization after training with rotated feedback, for both types of movements. However, the change after passive placement accounted for two thirds of the change after active placement. Under Bayesian integration of proprioceptive and predictive contributions, both are weighted approximately equal. Consequently, the contribution of felt limb position, or proprioception, to state estimates used in motor performance appears to be much larger than previously thought.

1-D-97 Modulation of visual-proprioceptive integration weights during reach planning due to stochastic reference frame transformations

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Based on a previous study (Burns&Blohm, 2010) introducing Head Roll (HR) will increase the variability of Reach Errors (REs). This data can be interpreted in two ways: first, signal-dependent noise (SDN) in HR estimation adds variability to the transformed signals and thus affects their Multi-Sensory Integration (MSI) weights. Second, MSI weights change due to uncommon HR postures instead of added noise in Reference Frame Transformations (RFTs). We designed an experiment to distinguish between these alternatives. Participants stood in front of a robotic setup and performed center-out reaches toward targets distributed on a 10cm circle, while keeping their gaze at the center. A conflict between visual and proprioceptive information occurred by shifting the hand 2.5cm while visual feedback indicated initial hand position at the centre. The task was with 3 HR, and 3 Neck Load (NL) conditions for each HR. For 0º HR, applying NL significantly shifted RE curves up/down and increased the variability; similar to HR. However, REs were more variable for changing HR (NL = 0) compared to changing NL (HR = 0). These results suggest that SDN in the internal estimate of HR induces variability into the RFTs and consequently MSI weights decreased for transformed signals when applying either HR or NL with a higher decrease for changing HR. These results confirm that RFTs should indeed be regarded as stochastic in nature and that previous results cannot be explained by unfamiliar postures. It also shows that noise in muscle spindles has an observable effect on RFTs underlying reach planning.

1-D-98 Role of muscle spindle feedback in the generation of the swing movement during walking in mice

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During walking, one step is divided in two phases. During stance phase, the foot is on the ground and provides propulsion. The foot moves from the anterior extreme position (AEP) to the posterior extreme position (PEP). During swing phase, the foot lifts off the ground after the stance at the PEP and moves towards the AEP to start the next stance. It is suggested that proprioceptive feedback form the muscle spindles (PFMS) are important for the precise leg movement during swing phase, However, the control mechanisms are not described. We measured kinematics of hind leg (HL) movements and electromyogram (EMG) activities from multiple muscles in mice during walking on a treadmill. The hind leg AEP (AEPHL) in wild type mice is on average 4mm (SD: 2mm) caudal to the PEP of the fore limb (PEPFL) and does not change (5±3mm, $p=0.09$) even if we mechanically disturb the ongoing swing phase that generates a well described stumbling corrective response. To address the role of PFMS during swing movement, we performed the same experiments with a mutant mouse line that lacks muscle spindles (Egr3-KO). In Egr3-KO, the average AEPHL-PEPFL distance is 1.4cm, significantly larger ($p<0.001$) and more variable (SD:5mm, $p<0.001$) than in wild types. When swing is disturbed in Egr3-KO mice the AEPHL-PEPFL distance does not change significantly, however the trajectory of the foot movement becomes more variable. Our data suggest that PFMS is important for the generation of the swing phase, by determining the foot trajectory, but the AEP can be determined by alternative mechanisms.

1-D-99 Investigation of the Relationship between Chronic Stress, Hearing Sensitivity and Noise-Induced Hearing Loss using a Rat Model

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Environmental and psychological stressors are known to affect hearing function. For example, acute stress increases hearing sensitivity, and also protects the inner ear from damage induced by loud noise exposure. At present, however, the role of chronic stress on hearing sensitivity and oto-protection remain uncertain. To that end, we used a previously-established model of daily restraint in rats to investigate the relationship between chronic stress, hearing sensitivity and noise-induced hearing loss. Adult male Sprague Dawley rats were divided into four groups: chronic restraint stress (6 h/day; 21 days), noise exposure (Day 14: 12 kHz tone at 110 dB SPL for 1 h), chronic restraint stress + noise exposure, and age-matched controls. Hearing sensitivity was assessed on Day 0 and Day 22 by measuring click, 4 kHz and 20 kHz auditory brainstem responses. Unlike acute stress protocols, chronic stress did not improve hearing sensitivity, as there were no differences in the ABR thresholds for the click or tonal stimuli between controls and chronically-stressed rats. Moreover, chronic stress did not offer protection against noise-induced hearing loss, as the noise exposure caused an equivalent shift in hearing thresholds in non-stressed rats compared to those chronically-stressed prior to noise exposure. Given that chronic stress is known to negatively affect neuron morphology in the auditory cortex, future studies are planned to investigate whether chronic stress, despite not affecting hearing levels, exacerbates noise-induced cortical plasticity.

1-D-100 Cortical Control of Olfactory Information Processing: The Role of the Anterior Olfactory Nucleus and Ventral Hippocampus in Vivo

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Sensory perception is not simply a feed-forward mechanism. Higher cortical regions actively modulate information processing in lower regions via diverse 'feedback' connections. This allows the cortex to suppress or enhance responses in peripheral structures depending on the relevance of the stimuli. In the context of the olfactory system, the anterior olfactory nucleus provides first-order feedback in the form of direct excitatory inputs to inhibitory interneurons of the olfactory bulb. However, the role of this feedback has not been directly demonstrated in awake behaving animals, leaving its relevance to olfactory processing elusive. To examine the behavioural function of olfactory cortical feedback, we virally expressed the chemogenetic activity modulators hM4D or hM3D bilaterally in CaMKIIa-positive neurons of the anterior olfactory nucleus pars medialis (mAON). We found that feedback from the mAON is capable of bidirectionally modulating olfactory sensitivity and performance on olfaction-dependent tasks. To reveal higher-order structures which may tune this bidirectional control of olfactory sensitivity, we infused the retrograde tracer cholera toxin subunit B in the mAON. As a result, we observed dense labelling in the field CA1 of the ipsilateral ventral hippocampus (vHPC). We further demonstrated that optogenetic stimulation of vHPC axon terminals at the mAON is sufficient to alter olfaction-dependent behaviours. Together, these results highlight an important behavioural gain-control function of the vHPC-mAON pathway among other roles they may serve in olfaction.

1-D-101 Concurrent reach and tracking adaptations of static and moving targets

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Given that the neural networks and behavioural parameters subserving saccadic and smooth pursuit eye movements are independent of one another, we wanted to explore whether a similar mechanism exists for ballistic reaching and tracking arm movements. Does adaptation to perturbed tracking movement generalize to that of a ballistic reach movement? Adaptation to perturbed tracking movements produced significant reach aftereffects although to a smaller extent; tracking aftereffects were about half the size (≈9°) of those produced after ballistic reach training (≈19°). In the second experiment, we looked at whether adaptation to tracking and reaching paradigms are independent of one another and would thus allow for concurrent adaptation to opposing perturbations (i.e. dual adaptation). Tracking trials were associated with a 30° CCW rotation while reaching trials were associated with a 30° CW rotation. We found significant reach aftereffects following dual training of ≈7°, which was substantially smaller than that produced when reach training was not concurrent with track training. The size of reduction of aftereffects is consistent with the extent of the interference from tracking training as measured by the reach aftereffects produced when only that condition was performed. These findings suggest that adaptation of tracking movements which tend to produce small errors that can be adjusted on-line, are processed somewhat although not completely independently of reaching movements which tend to produce larger errors that are adjusted on a trial-by-trial basis.

1-D-102 Characterisation of spinofugal nociceptive neurons via new genetic tools

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Farin B. Bourojeni (1,2), Artur Kania (1,2) 1 Institut de recherches cliniques de Montréal; 2 McGill University Pain is an unpleasant sensation that is vital for the maintenance of the integrity of our bodies.

Primary afferents relay nociceptive information from the periphery to higher brain regions via second-order neurons in the spinal cord. This system enables us to respond rapidly to noxious stimuli, to discriminate between them and to 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 spinofugal projection neurons. The Hoxb8:Cre mouse line expresses Cre recombinase in dorsal root ganglion and spinal neurons and using an axonal Cre reporter we visualized Hoxb8:Cre spinal neuron innervation of supraspinal regions. Hoxb8:Cre neurons innervate the parabrachial nucleus, periaqueductal gray, and thalamus. However, other nociceptive areas such as the amygdala and the septal nucleus are spared. The heterogeneous neurotransmitter identity of such termini reveals further molecular diversity spinofugal projection neurons. The Hoxb8:Cre line also allows us to study the time course of the development of supraspinal target innervation in an anterograde manner revealing that it starts in late embryonic stages and continues postnatally. Our experiments provide evidence for the genetic diversity of spinofugal neurons, and identify genetic handles to be used in functional analysis of nociceptive circuits.

1-D-103 Transsaccadic integration of spatial frequency information in an fMRIa paradigm

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To date, the neural correlates of feature information integration across saccades (i.e., transsaccadic integration, TSI) are relatively unknown. Using fMRI adaptation, we found that right inferior parietal lobule (IPL; specifically, SMG) and extrastriate cortex (putative V4) are sensitive to objet orientation in a space-fixed reference frame (Dunkley et al., submitted). Here, we used fMRIa to uncover the cortical correlates of spatial frequency in a space-fixed reference frame. Functional data were collected across 11 participants while they observed a vertical grating of a given spatial frequency in the center of the screen, followed by a grating at the same ('Repeat' condition) or different ('Novel' condition) spatial frequency. Participants were required to either fixate in the same position (Fixation task) or to make a saccade to the opposite fixation point (Saccade task). Participants were instructed to decide via a 2AFC task if the subsequent grating was repeated or novel. The Saccade task produced specific, significant ($p<0.05$) adaptation (novel>repeated; repetition suppression, RS) in FEF, SMG, cuneus and V2. The Fixation task produced specific, significant ($p<0.05$) adaptation in SMA. M1, LS, IPL and LOC show RS effects in both Fixation and Saccade conditions. Repetition enhancement (repeated>novel) effects ($p<0.05$) were observed in MFG during the Saccade task, whereas RE was observed ($p<0.05$) in SFG during the Fixation task. Overall, TSI of spatial frequency activated different regions within an occipito-parieto-frontal network in the Saccade vs. Fixation tasks.

1-D-104 Colour Modulates Inhibitory Control

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Actions are informed by a complex interaction between sensory inputs, attentional networks, behavioural goals and behavioural execution and inhibition networks. Taken together, these processes form what are known as the executive functions. Recent investigations have shown that colour can automatically bias object selection in visual search and in smooth pursuit target selection according to a hierarchy of red, green, yellow and blue. To date, the colour hierarchy has not been extended to inhibitory control. As such, we used the stop-signal paradigm to determine whether the attentional

priority for red enhances behavioural inhibition and execution. In one experiment, participants responded to red, green or white arrows and were required to countermand their response when an auditory signal was presented. There was no differential effect of colour on response execution or response inhibition time. In a second experiment, participants responded to white arrows and countermanded their response when the arrow changed to either red or green. In experiment two, participants countermanded their response when presented with the red stop-signal approximately 25ms faster than they did to the green stop-signal. In other words, red modulated inhibitory control but it did not facilitate responding. These results suggest that prefrontal decision-making networks dynamically access task relevant features. Future experiments will test this hypothesis further by making color relevant to the go signal and determining whether that will produce modulation of reaction times.

1-D-105 Assessing the Effects of Deafness on the Neuroanatomical Projections to the Second Auditory Cortex (A2) of the Cat

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When one sensory modality is absent, compensatory advantages are evident in remaining modalities. These advantages are thought to reflect recruitment of cortical areas that typically process stimuli from the missing modality. For example, evidence suggests that auditory areas contribute to enhancements in the visual domain following deafness. Interestingly, while the fractional volumes occupied by many auditory cortical fields are diminished following hearing loss, the second auditory cortex (A2) undergoes an expansion; however, the nature of the changes in neural connectivity that underlie this expansion remains unknown. This study examined how thalamic and cortical projections to A2 are altered following deafness. A retrograde tracer (BDA) was deposited into A2 in normal hearing, early-deaf, and late-deaf cats. Coronal sections at regular intervals were observed, and all neurons showing positive retrograde labeling were counted. Labelled neurons were assigned to functional cortical and thalamic areas according to previously documented criteria. The proportion of neurons in each area was quantified relative to the total number of labeled neurons. ANOVAs and posthoc tests were performed to identify changes in labeling patterns. Following the onset of hearing loss, changes in the pattern of labelled projections to A2 were observed both within the auditory modality and between sensory modalities. Results show that the patterns of thalamo-cortical and cortico-cortical projections to the second auditory cortex are altered following hearing loss in an age-related manner.

1-D-106 Effector-specific cortical mechanisms for memory-guided reaches and saccades: progression from target memory through motor planning and execution

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The human brain areas involved in reach and saccade planning have been studied extensively, but the effector-specific mechanisms underlying target representation, motor planning, and motor execution have not been clearly differentiated. In this study, we used an event-related fMRI design that temporally separated the major stages of memory-guided reaching and saccades into three distinct phases: visual target representation, motor planning, and motor execution. In each trial, subjects (N=12) fixated at midline and were briefly shown a target located between 4-7 degrees to the left or right of the midline. After a delay of 8 seconds (the effector-independent target representation phase), subjects were instructed with an auditory cue to perform a reach or a saccade. This was followed by a second delay of

8 seconds (the effector-specific motor planning phase). Finally, an auditory 'go signal' prompted subjects to perform the instructed movement by reaching-to-touch a touchscreen with their right hand or performing a saccade (the effector-specific motor execution phase). Our analysis to date indicates that during both motor planning and execution, bilateral reach-related areas in parietal (pIPS, mIPS) and frontal cortex (M1, PMd) are active. For saccades, bilateral saccade-related motor areas (mIPS, AG, FEF) are active during motor execution, but not motor planning. These preliminary results indicate that a cortical preference for reaches emerges during movement planning, whereas planning for saccades only emerges during motor execution.

1-D-107 Changing the form of feedback (error-based verse reinforcement-based) leads to dissociable motor adaptation.

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For error-based learning, it is suggested that adaptation occurs by minimizing error to update an internal model [1]. For reinforcement-based learning, it has been proposed that adaptation occurs by sampling motor outputs to find a set that maximizes success (hitting the target) [1]. Statistically, minimizing (squared) error or maximizing success corresponds to the mean and mode of a probability distribution, respectively [2]. Here we used a skewed noise distribution to corrupt feedback in order to separate the location of the mean and mode. We hypothesized that changing the form of feedback (error or reinforcement), when corrupted by skewed noise, would lead to dissociable motor adaptation. Participants grasped a robotic handle and reached to a virtual target. Vision of the arm was occluded. Feedback was provided only at the target and indicated true hand position plus a lateral shift drawn from a skewed distribution. This feedback was either an error signal or a reinforcement signal. The error group was presented with a single white dot at the location where the (displaced) cursor passed the target. The reinforcement group was presented with a binary signal (visual, auditory and monetary components) indicating whether they hit the target. We found that the error and reinforcement groups compensated for their estimate of the skewed mean and mode, respectively. These results show that reinforcement-based and error-based learning can occur independently and are dissociable. [1] Izawa et al. (2011) PloS Comput Biol. 7(2), e1002012. [2] Kording et al. (2004) PNAS. 101(26)

1-D-108 Wii Balance Board and Modified Balance Error Scoring System to assess changes in postural balance in young-adult male hockey athletes over athletic season

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To appropriately interpret postural balance in concussion assessments clinicians must understand how this may change throughout an athletic season. As a cost effective and portable system, the Wii Balance Board (WBB) can be used efficiently as a balance measurement tool by measuring range of centre of pressure (COP) and recovery time after perturbation. This study used a customized WBB computer game to quantify changes in recovery from virtual perturbation at 3 times in an athletic season. To test the validity of the WBB system, correlations between modified Balance Error Scoring System (mBESS) and WBB data were assessed. 22 male participants performed balance assessments using the mBESS, a WBB computer game, and the mBESS while standing on a WBB. Participants completed the mBESS according to standard protocol. During the WBB computer game, COP was represented as a dot on a laptop screen using a customized LabVIEW program. In each trial (n=5) a target moved in random sequence among

eight cardinal and ordinal directions. Participants were instructed to redistribute their weight on the WBB to meet the target dot with their COP dot. Recovery time and force data were recorded. There were differences in recovery time to virtual perturbation between baseline and mid-season time points ($p<0.05$). There was a significant difference in the variance in COPx for the single-leg mBESS condition ($p<0.005$). No difference was observed in raw mBESS scores. This study demonstrates the importance of considering progression of athletic season when interpreting balance measurements.

1-D-109 Brain Plasticity after Concussion in Young Rats: Brain Change without Behavioural Change

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Without a keen sense of balance and a lot of adventurous play children have a high risk of mild traumatic brain injury (mTBI). Often children appear to be healthy not long after a concussion but some suffer long term consequences. As a child develops, their brain goes through many changes and an injury may interrupt brain development. This study examines the effect of mTBI on development in juvenile Long Evans rats through observable differences in play behaviour and brain derived neurotrophic factor (BDNF). BDNF is a protein in the brain that aids in the survival of neurons and is related to experience driven plastic change. Half of the animals received a concussion-like injury over the right motor cortex and the others experienced a sham procedure. Two days later, play was recorded to observe differences in social behaviour. Tissue from the injured area (right motor cortex), the contralateral area (left motor cortex), and an unaffected area (medial prefrontal cortex) were analyzed for levels of BDNF as the brain is responding to the injury. BDNF was significantly higher in the injured and contralateral areas of the injured animals than in the same areas of the sham animals. There were no significant play behaviour differences between groups. These results emphasize there is an underlying recovery and compensatory process going on in the brain in the injured area and contralateral area. There were plastic changes in response to mild concussion without behavioural impairment. Supported by The Children's Hospital Research Institute of Manitoba

1-D-110 The role of conjugate eye movements to symmetric disparity stimuli

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The hypothesis that separate neural mechanisms control ocular convergence and divergence is explored. A target shifting in depth typically elicits a saccadic-vergence response (asymmetric vergence). Only when a target shift occurs directly along the midline can a purely symmetric vergence response result. The frequency of asymmetric responses to symmetric stimuli will be examined and compared to the dynamic properties of the symmetric movements. 4 adults completed the study. Symmetric vergence steps of 2˚ and 4˚ were dichoptically presented via a haploscope while eye movements were tracked using a video-based eye tracker (EyeLink 2). Stimuli were presented randomly, 30 times each, over four visits. Symmetric vergence responses were characterized by gain and peak velocity, and compared to the frequency of asymmetric responses at each stimuli level. Symmetric convergence response velocities were faster, $F(1, 3) = 33.2$, $p = 0.01$) and had a greater gain $F(1, 3) = 11.4$, $p = 0.04$) than divergence responses. Asymmetric vergence occurred more frequently to divergent stimuli ($p = 0.004$), while symmetric vergence occurred more frequently to convergent stimuli ($p=0.002$). The faster convergence system demonstrated significantly more symmetrical vergence movements. The greater

number of asymmetric vergence responses in divergence provides further support for the existence of different neural control mechanisms. This may represent an oculomotor adaptation designed to compensate for a slower, weaker divergence mechanism that is unable to produce the required symmetric motor response.

1-D-111 Tonic Endocannabinoid Signaling Controls Excitatory Drive in the Superficial Lamina (I/II) of the Mouse Spinal Cord

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Endocannabinoids (eCBs) are a widely expressed class of lipid signaling molecules, of which, Anandamide (AEA) and 2-arachidonyl glycerol (2-AG) are best described. AEA and 2-AG act as retrograde messengers and activate cannabinoid 1 (CB1) receptors to influence synaptic transmission and plasticity. By modulating synaptic transmission, the eCB system has been implicated in the regulation of various physiological functions and behaviors, including pain. Anatomical studies have established that CB1 receptors and the enzymes required for the synthesis and degradation of eCBs are expressed in lamina I/II of the spinal cord dorsal horn (DH), a region transmitting pain information. The precise mechanisms by which the eCB system controls synaptic function within lamina I/II remain unclear. We performed whole cell recordings of lamina I/II neurons and examined the role of tonic eCB signaling in the regulation of glutamatergic synaptic transmission. CB1 antagonist/inverse agonist AM251 increased the frequency but not the amplitude of spontaneous and miniature excitatory post synaptic currents (EPSCs), indicating that eCBs controls basal glutamatergic synaptic drive. Unexpectedly, when we examined the effect of AM251 on the amplitude of EPSCs evoked by stimulation of the dorsal root entry zone, we found that AM251 exerted two opposing effects. As expected, in one set of neurons, AM251 potentiated EPSC amplitude. However, in another set of neurons, AM251 induced a long-term depression (LTD) of EPSC amplitude. The mechanism underlying the observed LTD is currently under investigation.

1-D-112 Connectivity of dI3 Interneurons during development of the mouse spinal cord

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Microcircuits controlling movements require constant sensory information in order to adapt to continuously changing conditions. dI3 interneurons (dI3 INs) are a class of spinal interneurons found in laminae V-VII of the mice spinal cord. dI3 INs are known to receive sensory information from both low-threshold cutaneous afferent input and muscle afferents, and to convey this information to motoneurons through glutamatergic excitation. By means of genetic silencing, dI3 INs were found to be involved in a microcircuit crucial for paw grasps and an important component of sensorimotor control of locomotor activity. Considering that hand control and locomotor control are known to evolve as the motor system develops, we asked how the connectivity of dI3 INs matures. Our goal is to study the connectivity of dI3 INs during the development of mice. To reach this goal, Isl1-Cre; Rosa26-YFP transgenic mice were divided into three age groups, post-natal, juvenile, and adult. Using immunohistochemistry, we sought to analyze how the following projections to and from dI3 interneurons develop: 1. Sensory inputs to dI3 INs (vGLUT1/GFP). 2. Spinal excitatory inputs to dI3 INs (vGLUT2/GFP). 3. Excitatory projections from dI3 INs to motoneurons (vGLUT2/GFP/ChAT). The results from our experiments provide comparative insights as to how a spinal microcircuit centered on a

particular cell class but mediating different forms of motor activity develops during the maturation of motor control.

1-D-113 Functional characteristics of putative premotor areas in the intact, awake cat

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The primate premotor cortex is divided into a number of functionally distinct sub-areas (Dum and Strick, Physiol. Behav. 77: 677, 2002). In the cat, evidence also suggests that there are several subdivisions of area 6, as well as of area 4 (Ghosh, J. Comp. Neurol. 380: 191, 1997). There is, however, little information on the functional characteristics of these subdivisions. In the current study, we trained two cats to walk on a treadmill and to step over obstacles attached to the moving belt. The cats were then implanted for chronic recording of single neurone activity. In each penetration, we recorded cellular activity during voluntary gait modifications. We then tested the receptive field (RF) of the cells and applied intracortical microstimulation (ICMS) both at rest and during locomotion. The RFs of cells in area 6 were frequently more complex than those of cells in area 4γ (MI, motor cortex), encompassing several body parts (e.g. forelimb and mouth). Similarly, ICMS sometimes generated more complex effects than did stimulation in area 4γ. Some parts of area 6 were as effective as M1 in modulating muscle activity during locomotion. While some cells in area 6 discharged primarily during the gait modification (as in MI), cells in some regions of area 6 discharged in a limb-independent manner several steps before the step over the obstacle. We suggest that these latter cells are implicated in the planning of the gait modification. Together, these preliminary results suggest that the cat's premotor cortex might comprise regions homologous to those described in the primate.

1-D-114 : Slow and fast nerves regenerate into appropriate endoneurial tubes to reinnervate tibialis anterior (TA) muscles after common peroneal (CP) nerve cut and repair; size-dependent branching occurs more distally in intramuscular sheaths

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Muscle fibers innervated by one nerve, a muscle unit (MU), identified with PAS staining after repetitive on-off fatiguing tetanic contractions, are located within defined MU territories in muscle cross-sections. The territories provide an indirect image of intramuscular nerve branching. MU contractile forces and muscle fiber numbers increase with size of their innervating nerves in normal and reinnervated muscles. It follows that extent of nerve branching as measured by MU territory, and nerve size must also correlate. Here we asked 1) is this prediction accurate in normal and reinnervated TA muscles? 2) If and how does the pattern of nerve branching within intramuscular (IM) nerve sheaths change after the known random axon regeneration into distal nerve stumps after CP nerve transection and surgical repair? And 3) Is the normal preference of slow nerves to reinnervate muscle fibers in the deep portions of skeletal muscles demonstrated during nerve regeneration? The answers were 1) Yes: although reinnervated MU territories are reduced in size, there is the same size-dependent relationships between reinnervating nerve size and extent of intramuscular branching, 2) Yes, the pattern of nerve branching was altered with significantly more MU fibers adjacent to one another in reinnervated muscles but, more distal regenerated nerve branching within the IM sheathes restored the normal size relationships despite the altered branching patterns and 3) Slow motor nerves demonstrated a preferential reinnervation of endoneurial tubes that had formerly contained these nerves.

1-D-115 Overexpression of the muscarinic receptors following visual training paired with cholinergic enhancement

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Cholinergic stimulation coupled to visual exposure to a specific stimulus enhances the long-term cortical response to visual stimuli. However, there are a variety of cholinergic receptors subtypes in the visual cortex that play distinct and sometime opposite roles in the modulation of V1 neurons. The weight of these different receptors in the different steps of cholinergic modulation of repetitive visual stimulation is still unclear. To determine which cholinergic receptors were involved in the increased cortical reactivity induced by cholinergic enhancement, RT-PCR was used. Cholinergic enhancement was performed either by an electrical stimulation of the basal forebrain or a pharmacological stimulation of the cholinergic system (donepezil, 1mg/kg, daily i.p. administration). A daily visual exposure of the rats to sine-wave gratings (training) was paired or not with this cholinergic enhancement. RT-PCR was performed at 10 minutes, one or two weeks of this training. The results showed a long-term increase of the mRNA expression of muscarinic subunits M3, M4 and M5 and nicotinic subunit α7 at 2 weeks of visual exposure but only when the visual exposure was paired with the donepezil enhancement. The expression of the receptors was not changed for any of the other time courses. This study shows that the muscarinic cholinergic receptors are involved in long-term changes sustaining perceptual learning.

1-D-116 Biologically Realistic Deep Supervised Learning

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Learning in multi-layer neural networks (deep networks) can be very powerful. Deep networks can achieve human-level performance on a range of tasks, and deep learning leads to emergent representations that resemble those in the neocortex. However, the most successful learning algorithms for deep neural networks invoke mechanisms that are not biologically realistic. To date, a biologically plausible mechanism for learning in deep networks has not been proposed. Here, we demonstrate a biologically realistic form of deep supervised learning that uses random synaptic weights in feedback connections to instruct lower layers about error gradients. Inspired by studies of neuronal circuits in the neocortex, our model utilizes stochastic spiking neurons with three functional compartments: a soma where spiking occurs, a basal dendrite which receives feedforward sensory information, and an apical dendrite which receives feedback from upper layers in the network. We show that our network can learn to classify hand-written digits with a high degree of accuracy, and take advantage of multiple layers to achieve greater performance than can be achieved by one or two-layer networks. The learning algorithm allows the hidden layers to learn useful features for classification. In addition, we provide specific experimental predictions about how apical dendritic inputs should shape plasticity in the neocortex. If evidence for a deep learning algorithm in the brain could be found, it would constitute a major advance in the unification of theory and biology in modern neuroscience.

1-D-117 Sensorimotor processing of ipsilateral and contralateral limbs in primary motor cortex

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Recent work has shown that primary motor cortex (M1) is surprisingly active for ipsilateral motor actions. In this study, we used mechanical disturbances to the limb during postural control to investigate

sensorimotor processing in M1 neurons related to both upper limbs. A non-human primate (NHP) stabilized cursors representing the locations of its right hand at a virtual target. After 1000-1500ms, flexor or extensor step torques were applied to the shoulder, the elbow, or both (9 load conditions). The NHP had 1000ms to return the cursor to, and stop at, the target. This task was repeated with the left arm, and then bilaterally with one target for each hand and loads applied to both arms simultaneously. We recorded and examined the activity of 167 M1 neurons using a micro-electrode array and 29 neurons from single electrodes. We found that a subset of neurons showed different pre-perturbation activity if the upcoming perturbation was going to be on the arm contralateral to the recorded neuron or bilaterally. Surprisingly, the activity of these neurons before an ipsilateral perturbation was similar to the activity before a bilateral perturbation. After perturbation onset, 73% of M1 neurons modulated their responses to contralateral perturbations, 40% to ipsilateral perturbations and 34% to either. When torques were applied to both arms at once, each neuron's activity corresponded to a vector sum of its modulation to torques on either arm alone. This work highlights that M1 activity reflects sensorimotor processing of contralateral and ipsilateral limb motor actions.

E – Homeostatic and Neuroendocrine Systems

1-E-118 Corticosteroid Binding Globulin Programming by Prenatal Predator Odour Exposure in Mice

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Corticosteroid binding globulin (CBG), key carrier protein of corticosterone (Cort), binds most of Cort in the plasma, leaving a small portion of unbound Cort that is biologically active. Thus, CBG is a key modulator of Cort availability in the plasma and hence the stress response. Studies in numerous species have shown that CBG levels decline in response to chronic stress. Prenatal stress is known to alter stress reactivity in offspring, however few studies have examined the impact of chronic prenatal stress on adult CBG programming. We used a naturalistic stressor in pregnant mice -chronic predator odour exposure- to examine stress reactivity and CBG levels in adult offspring, at baseline and after exposure to an acute restraint stress. Prenatally stressed (PS) males, but not females, had a consistently higher maximum CBG binding capacity in the plasma, indicating higher CBG levels, accompanied by lower free Cort levels compared to controls. However, total Cort levels were similar between groups. Despite lower free Cort levels in PS males, they exhibited a more rapid increase in free Cort in response to restraint from 0-60 min of stress relative to controls. The high plasma CBG levels in PS males were also mirrored in the liver, with higher CBG mRNA levels than controls. Our study is the first to show that prenatal stress increases CBG levels in adulthood in males, but not females, in both plasma and liver. It highlights the critical importance of measuring plasma CBG and Free Cort and examining how prenatal stress impacts adult CBG levels and the response to stress.

1-E-119 Glycemic condition influences subfornical organ neuron responsiveness to angiotensin

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The subfornical organ (SFO) is a sensory circumventricular organ implicated in the regulation of energy and fluid balance. SFO neurons have been shown to respond to both glucose and angiotensin II (ANG) - circulating signals traditionally classified as energy and cardiovascular regulating signals, respectively.

The purpose of this study was to investigate the integration of glucose and ANG signals in the SFO by assessing the excitability of SFO neurons in response to bath application of ANG in either hyper- or hypoglycemic environments. SFO neurons from Sprague-Dawley rats (male; 21- 35 days) were micro-dissected, dissociated into individual neurons, plated, and incubated at either 1, 5, or 10mM glucose. Subsequently, perforated-patch & current-clamp recording techniques were used to assess the effects of bath application of ANGII (10nM) on membrane potential at either 1, 5, or 10mM glucose concentrations. Our results show that at 10mM glucose, 67% of SFO neurons tested cause a depolarization of the membrane potential in response to bath application of ANG (10nM) (MP Δ= %2B 7.2 mV ± 1.1 mV; n=6/9). In contrast, at 1mM glucose only 33% of neurons tested responded to ANG application (MP Δ = %2B 6.2 mV ± 2.2 mV; n=4/12). These data suggest that single SFO neurons are able to integrate both of these traditionally classified energy and fluid balance signals, and that glycemic state may alter the regulation of fluid balance and cardiovascular function at the SFO.

1-E-120 MicroRNA involvement in estradiol-mediated synaptic plasticity

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Estrogens have long been known to affect synaptic plasticity. The mechanisms underlying these effects remain incompletely understood. MicroRNAs (miRs), a class of small, non-coding RNAs, have been implicated in a number of processes in the central nervous system including differentiation and synaptic plasticity. Estrogens influence miRNA expression in hormone-responsive tissues such as the breast and uterus. However, very little research to date has focused on whether estrogens influence miRs in the brain. MiRs present a potential mechanism for the action of estrogens on synaptic plasticity. To determine the effects of estrogens on hippocampal miRNA expression, female CD1 mice were ovariectomized and treated 7-10 days later with the oil vehicle or 3 µg/kg estradiol (E2). Mice were euthanized 40 min, 6 h or 12 h post-injection, hippocampi were removed. Total RNA was extracted and 2µg of good quality RNA from 6 hour animals was subjected to next-generation sequencing of small RNAs. Following analysis, 4 miRs were shown to significantly change following E2 administration. Results were validated by qPCR, showing a significant difference between vehicle and E2-treated animals. However, vehicle animals also showed a significant difference from untreated controls. These results suggest an effect of the stress of injection on microRNA expression that is prevented by E2 treatment. Stress has been shown to decrease dendritic complexity in CA3 of the hippocampus, and this effect can be reversed by E2 treatment.

1-E-121 Hypothalamic CRH neurons orchestrate stress induced behaviours

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We exhibit wide-ranging behaviors following stress. These span from immediate survival behaviors to hyper-vigilance to self-referential activity in a temporally organized fashion and faithfully reflect the challenges of the environment. In rodent models these stress induced behaviors include grooming, rearing and freezing. Here using cell-type specific manipulations and meticulous behaviour analysis, we show that the same neurons that are the principal controllers of the hormonal response to stress, the hypophysiotropic CRH neurons, determine the behavioral pattern emerging after stress independently of corticosterone. Silencing CRH neurons after footshock inhibits grooming while promotes rearing and locomotion. On the other hand in the absence of stress, photostimulation of CRH neurons is sufficient to

increase self-referential grooming behaviour and curtail other behaviours. Activation of this circuit circumvents environmental cues and shifts behavioural strategies towards self-referential grooming behaviour even in situations that are threatening or favour greater vigilance. Furthermore utilizing anatomical tracing and electrophysiology we have identified the pathway from the paraventricular nucleus to the lateral hypothalamus through which CRH neurons regulate behaviour. Our observations provide a new model that can be exploited to better understand the circuit function/dysfunction underlying syndromic behaviors linked to psychiatric and neurodevelopmental disorders.

1-E-122 Weight Loss in the 5XFAD Mouse Model of Alzheimer's Disease: A Behavioural and Hormonal Analysis

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The 5xFAD mouse is a double transgenic model of Alzheimer's disease (AD). Weight-loss is an issue in human AD patients, and age-related weight-loss is also seen in 5xFAD mice. We investigated age-related changes in body weight, feeding behaviour, activity levels, frailty, feeding-related hormones, leptin, hormone sensitive lipase (HSL) and uncoupling protein-1 (UCP-1) mRNA in female 5xFAD mice and their WT (B6SJL/J F1) controls from 3 to 12 months of age. At 9 and 12 months of age, 5xFAD mice weighed less than WT controls ($p<0.05$), but WT ate more than 5xFAD mice ($p<0.05$). 5xFAD mice exhibited less rearing and climbing ($p<0.05$), and remained still longer than WT mice ($p<0.05$) but there were no genotype differences in the frequency of jumping and grooming. 5xFAD mice had higher frailty scores than WT mice ($p<0.05$) and different food presentations (food on hopper, food in cage, or mashed food) had no effect on frailty score. 5xFAD mice had less white adipose tissue than WT mice ($p<0.05$), but the amount of brown adipose tissue did not differ between genotypes. Expression of mRNA for leptin and HSL were reduced ($p<0.05$) and expression of mRNA for UCP-1 was elevated ($p<0.05$) in 5xFAD mice. Our data suggest that compared to WT mice, 5xFAD mice are hypoactive and have a higher frailty index that was not decreased by changing their mode of food presentation. 5xFAD mice also have less fat and express less leptin and HSL mRNA but express more UCP-1 mRNA than WT mice, indicating elevated fat burn and reduced adipogenesis in these mice.

1-E-123 Optogenetic manipulation of clock driven activity in the OVLT

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The Organum Vasculosum Lamina Terminalis (OVLT) is one of the key players in osmoregulation in animals. In instances of hyperosmolality, OVLT neurons become electrically excited and promote the sensation of thirst by activating dipsogenic regions of the prefrontal cortex. Recent work has shown the occurrence of need-free water intake during the last two hours of the active period (PSP; pre-sleep period) in mice. In this study we test our hypothesis that this behaviour is driven by the release of vasopressin (VP) from the axon terminals of Suprachiasmatic Nucleus (SCN) neurons that project to the OVLT. Cell-attached recordings show that SCN-VP and OVLT neurons significantly increase their firing during the PSP. Electrical stimulation of the SCN caused release of endogenous VP within the OVLT, as detected by HEK cells transfected with the VP V1a receptor and the Ca2+ reporter GCaMP6m. Release of VP in the OVLT could also be detected following optogenetic activation of SCN-VP terminals in VP-Cre/Lox-P ChETA mice. Optogenetically induced VP release also excited OVLT neurons prior to PSP, and

this effect could be antagonized by a selective V1a receptor blocker. Additionally, the increase in firing rate displayed by OVLT neurons during the PSP could be suppressed by inhibition of SCN-VP terminals in slices prepared from VP-Cre/Lox-p ArchT mice. These results indicate that the enhancement of firing rate of OVLT neurons during the PSP is specifically dependent on VP release from SCN-VP terminals.

F – Cognition and Behavior

1-F-124 Circuit principles of neuronal processing in larval drosophila melanogaster thermotaxis

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An important goal of systems neuroscience is to understand the computational process by which neural circuits use sensory information to generate adaptive behaviors. Drosophila larvae avoid excessively cool temperatures using a small set of sensorimotor transformations regulating the frequency and outcome of navigational decisions. During each navigational decision, larvae sweep their head from side to side, gathering thermal information that informs the choice of a new direction for forward movement. Automated trajectory and posture analysis of individual animals navigating temperature gradients enables us to quantify navigational decisions of each animal. We have identified two distinct groups of projection neurons that when inactivated exclusively modulate individual navigational decisions, such "which way to turn" and "when to turn". We mapped the "hits" from the behaviorally screen using EM reconstruction and found they receive direct synaptic inputs from cold sensing neurons. We then mapped all of their downstream partners using EM reconstruction identifying key candidate descending neurons that project to nerve cord. We are currently characterizing the computational dynamics of these elements of larval navigation circuits by measuring and manipulating neuronal activity in freely moving and/or restrained animals using novel methods in optical neurophysiology.

1-F-125 Utility of a Reading Span Task in assessing cognition in early-phase relapsing-remitting multiple sclerosis

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Background: It is well established that cognitive impairment is present in over half of people with MS (PWMS). Working memory (WM) is commonly impacted in PWMS and can be assessed using reading span tasks (RST). These tasks involve reading a phrase, making a decision about the phrase, stating a letter aloud, and then remembering a series of letters after a predetermined number of sentences. Thus, these tasks assess a person's ability to hold information in mind while being distracted. Objectives: To determine if RST can discriminate between PWMS and healthy controls (HC), to establish its psychometric properties and determine if performance changes over time. Methods: Seventy PWMS recruited from the Ottawa Hospital MS Clinic were matched to 72 healthy controls on age, sex and education. Participants completed the RST at baseline and three-year follow-up (32 MS and 32 HC) as part of a larger battery of tests. Results: PWMS performed significantly worse than HC on the RST at baseline and follow-up. On the RST 8.6-14.3% were impaired on the various RST subtests at baseline and 3.1-12.5% were impaired at follow up. Performance on the RST remained generally stable over the

three-year interval. Conclusions: RST discriminated between PWMS and HC and identified impairment to a comparable degree as previously validated measures of WM. The low frequency of impairment on WM measures in this study is likely due to unique characteristics of this sample. The stability of WM performance over time likely reflects the subtlety of cognitive dysfunction early in the disease.

1-F-126 Differences in neural circuits activated by safety learning or fear extinction in rodents

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The ability to differentiate between safe and dangerous environments, and to adjust behavior accordingly, is critical to survival. Safety learning involves associating distinct environmental stimuli (safety signals) that predict the non-occurrence of aversive stimulation. Once learned, these signals inhibit fear responses. In contrast, extinction learning is an active relearning process that involves repetitive exposure to non-reinforced cues that were once associated with presentation of threat. Although both fear extinction and safety learning lead to a reduction in fear, the potential neurobiological processes that support these forms of learning may be distinct. To address this, we set out to comprehensively compare the neural circuitry involved in fear conditioning, safety learning and extinction by performing functional mapping of the IEG product c-fos. Ten rats underwent three days of conditioning in which animals received five presentations of a tone that always co-terminated with a mild shock. An additional ten rats underwent three days of safety learning whereby the five tones were never correlated with the shock. Following the last training day, half of the animals were returned to the conditioning context and freezing to three tones was examined. As expected, rats undergoing safety training showed lower freezing during presentation of the test tones compared to fear conditioned rats. Rats were euthanized 90-minutes later and preliminary analyses found that safety training altered neural activity in the medial prefrontal cortex--a region known for fear inhibition.

1-F-127 Effects of forced swimming in neonatal rats with excitotoxic lesion in the corpus callosum

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Approximately 10% of newborns are premature, and most of them have brain injuries such as periventricular leukomalacia (PVL), causing ventriculomegaly with necrosis in the external angles of lateral ventricles, produced by the loss of white matter due to cell death of oligodendrocyte progenitors which are susceptible to excitotoxicity. In this study we used neonatal rats (Sprague Dawley); for excitotoxicity injury we administered N-methyl-D-aspartate acid (NMDA) (2 µg/µl) in the corpus callosum at postnatal day 5. Vehicle solution was administered as a control. Half of the animals were forced to swimm for 10 min, twice a day, for 24 days starting on postnatal day 7; the other half remained in their home cages. We evaluated the spontaneous motor activity and ability to habituate to their environment on postnatal days 25, 30, and 40; the rats were sacrificed on postnatal day 41. Lesions alone produced ventriculomegaly and hyperactivity, but the latter was significantly reduced by forced swimming; all of the groups showed habituation. We thank Jorge Larriva, Araceli Espinosa-Jeffrey, Rogelio Arellano, Roberto A. Prado-Alcalá, Norma Serafín, Cristina Medina, Leonor Casanova, Martin García, Alejandra Castilla, Deisy Gasca, Lourdes Palma, Nydia Hernández, for technical assistance. Supported by CONACyT (218556-166772 and scholarship 621147/331013) and PAPIIT-UNAM (IN621147 and IN202414)

1-F-128 The Relationship between Schizotypy and the Propensity to Accept Extraordinary Social Roles

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Background: Delusions of grandeur are frequent in schizophrenia and psychosis. They exist to a lesser extent in the general population, but reveal a will to play extraordinary roles (e.g., being a prophet). Given that cognitive and behavioral strategies associated with such a will could conflict with those involved in playing more ordinary roles, one can ask whether this propensity contributes to some symptoms, such as behavioral disorganization. We thus tested if the will to play extraordinary roles in healthy participants could predict some schizophrenia-like traits. Methods: 209 healthy volunteers between the ages of 18 and 30 were recruited to fill out questionnaires assessing schizotypal traits, including the schizotypal personality questionnaire (SPQ). They were then presented with hundreds of names of social roles and asked to decide, for each role, whether or not they would consider playing it at any moment of their lives. Results: Participants accepting a greater percentage of the extraordinary roles, regardless of the favorability of these roles, had higher SPQ scores. This correlation ($r = .401$, $p = 7.17E-09$) was significantly greater than the correlation between the percentages of ordinary roles accepted and the SPQ scores ($r = .145$, $p = .044$) (Fisher Z-transform, $p = .003$). Among the three factors of the SPQ, disorganization was the one best predicted. Conclusions: The correlations found here should prompt further studies to investigate whether the will to play extraordinary roles could be a contributor to the symptoms accompanying psychosis and schizophrenia.

1-F-129 The role of the cholinergic midbrain in sensorimotor gating

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Sensorimotor gating is a pre-attentive process that suppresses sensory evoked motor responses in favour of an orienting response towards a sensory stimulus. We study this using prepulse inhibition (PPI) of the acoustic startle response. PPI occurs when the presentation of an acoustic prepulse inhibits the processing of the startling stimulus, resulting in a reduction of startle magnitude. It is hypothesized that the principle mechanism underlying PPI is cholinergic inhibition by the pedunculopontine tegmental nucleus (PPT). To test this, we injected transgenic rats (Chat-Cre) with either a DREADD (rAAV8-hSyn-DIO-hM4Di-mcherry, N=9/group), optogenetic (rAAV5-EF1a-DIO-ChR2(H134R)-EYFP, N=3/group) or respective control virus in the PPT. Chemogenetic inhibition of the PPT did not disrupt PPI at both prepulse levels (75 or 85 dB SPL) or across all interstimulus intervals tested (ISI: 15, 30 or 100 ms). We did see a trend toward reduced baseline startle with CNO administration compared to vehicle. Conversely, optogenetic stimulation of the PPT was unable to induce PPI. During certain trials of PPI testing we replaced the auditory pre-pulse with a light stimulation of the cholinergic cells of the PPT. During these trials we saw a facilitation of startle in the ChR2 expressing rats. This was most robust at the ISI of 15 ms. This facilitation was absent when animals were re-tested with a nicotinic antagonist. Although the data is preliminary, our conclusions suggest that the cholinergic cells of the PPT may not be as critical for PPI as generally assumed.

1-F-130 Characterization of Hippocampal Inhibitory Stress Circuitry using Optogenetics

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Stress initiates the release of glucocorticoid hormones (GCs) by activating hypothalamic-pituitary-adrenal (HPA) axis which then triggers diverse adaptive physiological and behavioral responses. During the emotionally stressful experience, the ventral hippocampus (vHPC) is believed to attenuate the HPA-axis activity by indirectly inhibiting the paraventricular nucleus of the hypothalamus (PVN). While much effort has been made to demonstrate the inhibitory influence of vHPC on the HPA-axis during psychogenic stress, the underlying neural pathway has not been directly studied. Using the pathway specific optogenetic approach in mice, we activated the vHPC inputs at the anterior hypothalamic nuclei (AHN) during a 30 min-physical restraint stress and examined its effects on stress-induced anxiety behaviours in the elevated plus maze, the successive alleys, and open field tests. Our findings suggest that the predominantly GABAergic AHN is the functional intermediary structure through which vHPC exerts its inhibitory control on stress-induced anxiety behaviours and physiological changes in respiration and circulating corticosterone level. Together, these results show an important top-down modulation of stress response by hippocampus-hypothalamus circuitry as a key element in the central feedback of HPA-axis.

1-F-131 Neuronal Pattern Separation in a Computational Model of Motion Discrimination

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In this study, we examine whether the process of neuronal pattern separation may drive the rapid discrimination of visual motion stimuli in the lateral intraparietal area (LIP). Starting with a mean-rate model that captures neuronal activity in LIP, we show that overlapping input patterns can be reformatted dynamically to give rise to separated patterns of neuronal activity. Using the model, we capturing key features of neural activity in LIP during a task of decision-making and propose that the heterogeneity of neural responses promotes accurate decision-making by generating signal correlations lower than input correlations, in turn leading to accurate stimulus discrimination. Finally, we test several predictions of the model in recordings of LIP data obtained from macaque monkeys performing a task of dot-motion discrimination. The model predicts that a key ingredient of pattern separation is the presence of heterogeneity in the response of individual units. Furthermore, the model proposes that pattern separation relies on heterogeneity in the temporal dynamics of neural activity and not merely in the mean firing rates of individual neurons over time. Predictions are confirmed in recordings of macaque LIP neurons and show that the accuracy of pattern separation is a strong predictor of behavioral performance. Converging evidence from computational, theoretical, and experimental analyses suggest that neuronal pattern separation based on heterogeneous activity in LIP underlies an important role in the accurate disambiguation of visual stimuli during rapid decision-making.

1-F-132 High-Throughput Behavioural Analyses to Bridge the Genotype-Phenotype Gap

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Bridging the genotype-phenotype gap remains a fundamental problem in biology. This gap is particularly wide with respect to understanding behavioural phenotypes given the sheer number of intermediary processes involved. However, combined with dimensionality reduction techniques, high-throughput

behavioural tracking systems lay the foundation for a phenomic understanding of behaviour. By parsing a multivariate behaviour into its component parts, the contribution of numerous genes to each component can be quantitatively assessed and the underlying gene networks may iteratively be assembled. Taking this approach, hundreds of mutant C. elegans strains were assayed along numerous morphological and behavioural phenotypic variables simultaneously. We found a number of previously unreported genes that affected spontaneous locomotion, response to mechanosensory tap, and body size. Further analysis revealed that many of these phenotypic variables vary continuously along a spectrum, suggesting that a complex genetic architecture underlies many seemingly simple phenotypes. Choosing mutants which manifested extreme phenotypes along these spectra (as compared to wild-type N2), we subsequently adopted a reverse genetic approach to validate and more thoroughly assay the contribution of these genes. Results will be discussed, focusing on the following phenotypes: spontaneous locomotor reversal, mechanosensory-evoked response, and body size. This work will serve to validate the contribution of a high-throughput tracking technology to phenomics.

1-F-133 Focused-Attention versus Open-Monitoring Meditation: An MEG investigation of the underlying oscillatory brain networks

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The phenomenology and reported effects of meditation vary according to the technique practiced. While numerous studies have explored the cerebral mechanisms involved in meditation, little research provides direct comparisons between the neuronal network dynamics involved in different meditation techniques. Here, we explore and compare brain signals recorded with magnetoencephalography (MEG) during (a) focused-attention meditation (FAM), and (b) open-monitoring meditation (OMM) in a group of expert meditators (12 monks). We also compare FAM and OMM relative to resting-state. To this end, we estimated MEG source time courses using minimum-norm and computed spectral power in multiple frequency bands (delta, theta, alpha, beta and gamma). In addition, we conducted connectivity analysis using imaginary coherence and weighted phase-lag index and computed graph theoretical measures and multifractal scaling parameters in both conditions. We also used machine learning algorithm techniques in order to see which features allows best to discriminate across conditions. Preliminary findings reveal several differences between FAM and OMM and also between meditation (OMM/FAM) and resting condition. Interestingly, OMM was associated with higher theta power in the right temporal pole. We discuss these results in the context of previous cognitive neuroimaging studies of meditation and we outline paths for future research.

1-F-134 A neuroactive bacteria attenuates stress-induced behavioural deficits and inflammation independent of restoring the gut microbiota

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The gut microbiota and the brain are engaged in continuous interplay--a phenomenon that influences host neural function and behaviour. However, the functional relationship between the microbiota and stress-induced changes in brain and behaviour remain unknown. Using a neuroactive strain,

Lactobacillus rhamnosus (JB-1), we investigated whether gut-brain signalling modulated changes induced by exposure to chronic stress. Mice administered JB-1 and subjected to chronic social defeat were assessed for behavioural deficits, while 16S rRNA sequencing was used to analyze the microbiota community. To investigate gut-brain communication, immunoregulatory and metabolomic alterations were examined. Chronic stress induced deficits in social and exploratory behaviours while increasing anxiety-like behaviour--changes that were attenuated with JB-1-treatment. Defeated mice exhibited markers of inflammation, such as elevated IL-6 and kynurenine levels, dendritic cell activation, and transiently elevated levels of IL-10+ T regulatory cells that were suppressed over time; these alterations were prevented by JB-1 administration. Stress-exposure altered the microbiota profile and reduced community diversity, none of which were restored by JB-1 treatment. These findings suggest an association between stress-induced behavioural deficits and alterations in the microbiota, and posit systemic changes as a consequence of microbiota-gut-brain communication. We also demonstrate that the beneficial effects of JB-1 are exerted independently of correcting structural dysbiosis in the microbiota.

1-F-135 A Comparison of Pre-Surgical Language Mapping Paradigms Between MEG and fMRI

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Goal. Our goal was to determine the correspondence for localizing language areas between MEG and fMRI while participants performed the same set of tasks. Methods. Nine healthy, right-handed adults (19-70 years old, 6 female) completed three tasks (sentence comprehension, word fluency, and object naming) in both MEG and fMRI on separate days. The tasks involved both expressive and receptive language processing. The MEG (Elekta Neuromag Oy, FL) data were epoched into individual trials based on stimulus onset, and conditions were contrasted in AFNI. For all fMRI (GE Medical Systems, Waukesha, WI) images, the stimulus timecourse was convolved with the hemodynamic response function as input to a general linear model for language localization. For each paradigm and modality, group activation results were generated in AFNI using 3dttest++. Results. Left-lateralized activation in critical language areas (e.g. Broca's and Wernicke's area) was reasonably consistent in both MEG and fMRI across the group and tasks. Depending on the task, group-level activation also occurred in the fusiform gyrus, visual areas, and motor cortex. MEG findings appeared more left-lateralized, with fMRI results demonstrating more bilateral activity in language areas. Conclusion. Both MEG and fMRI localize language areas in the brain. However, given the different physical properties that each modality measures, the paradigms for each modality should be optimized, and cautiously interpreted for clinical use since neither provides a complete picture of the language network.

1-F-136 Representational similarity analysis of category-related recognition-memory signals in the human medial temporal lobe

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Neuropsychological studies in patients and functional neuroimaging work have established that perceptual representations of complex objects in the visual ventral stream are shaped by semantic category membership. Whereas the categorical structure of these representations has been well characterized in the context of perceptual tasks, much less is known about the organization of corresponding memory signals, specifically in the medial aspects of the temporal lobe (MTL), which

includes the perirhinal, parahippocampal, and entorhinal cortices, as well as the hippocampus. In the current study, we used high resolution fMRI, in combination with multi-voxel pattern analysis, to examine representational similarities in distributed patterns of activity in the MTL during memory judgements for images of real-world objects. Specifically, participants performed a continuous recognition memory task on visually presented objects from 12 different categories, which were matched for recognition accuracy. On each trial, their task was to determine whether the object presented was new (1st presentation) or had been encountered before (2nd presentation). Preliminary results show evidence for category-specific representations across the different structures that comprise the MTL. This suggests that category structure is differentially preserved in recognition-memory signals in MTL structures, offering support for the notion that its influence extends beyond perceptual representation.

1-F-137 Cognitive Function as Related to Cumulative Head Impact Exposure in Football: Effects of Position

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Repetitive sub-clinical head impacts (SHI) are linked to progressive cognitive decline and post mortem chronic traumatic encephalopathy (CTE) diagnoses in professional contact-sport athletes. Given positional variation in SHI exposure profiles and CTE diagnoses in football, our objective is to determine the influence of SHI exposure profile on cognitive function. In 2014 and 2015, we assessed the cognitive function of 63 male varsity football athletes in the pre- and post-season periods. Cognitive battery scores (www.cambridgebrainsciences.com) and reaction times were assessed both in terms of season-long changes, and in comparison to controls as a representation of athletes' cumulative SHI exposure. There was no difference between pre- and post-season battery scores or reaction times for any of the positions played suggesting that a single season of SHI exposure does not cause significant cognitive decline. When considering all data as a representation of career-long SHI exposure, footballers had impaired scores relative to the general population in the pre-season. Further, wide receivers (few high magnitude impacts) demonstrated the fastest reaction times and consistently outperformed defensive linemen (frequent low magnitude impacts). Collectively, these results align well with previous biomechanical and clinical literature and suggest that there is a continuum of cognitive function impairments across positions and SHI exposure profiles. Better characterization of this relationship may help guide participation, coaching strategies, and safe play decisions in sport.

1-F-138 Concussion Does Not Affect an Athletes Ability to Inhibit a Motor Response

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Concussions are associated with negative alterations in executive function (1, 2). Response inhibition is a key brain function that can be transiently impaired following a concussion (3, 4), however current findings on response inhibition are inconsistent. We used a complex sensorimotor task to investigate the effects of acute concussion on the ability to inhibit a motor response. Subjects used 2 robotic arms to hit two virtual target shapes on a 2D screen and avoid other non-target shapes. Subjects performed this task in a pre-season test, and in serial follow-ups at 3 days, 2 weeks, and 1 month post-concussion. 4 athletes sustained a concussion during the season. One-way repeated measures ANOVAs indicated task performance did not significantly differ across time for all variables including: task accuracy ($p=0.120$);

target hits (p=0.099); distractor hits (p=0.272), and aborted distractor hits (p=0.742), hand velocity upon target contact (p=0.414), and hand velocity upon distractor contact (p=0.488). These preliminary results show that response inhibition is unaffected during a complex sensorimotor task after a concussion and may also suggest minimal damage to the specific brain regions responsible for response inhibition following a concussion. 1. Echemendia et al. (2013), Br J Sports Med; 2. Howell et al. (2013), Med Sci Sports Exer; 3. DeHaan et al. (2007), Neuropsychologia; 4. Mayr et al. (2014), PloS One.

1-F-139 Examining the effect of chronic intranasal oxytocin administration on the neuroanatomy and behaviour in two different autism-related mouse models

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Introduction: Autism is a neurodevelopmental disorder characterized by social communication deficits and repetitive behaviors. Oxytocin is known for its ability to promote social behaviours and may be a promising therapeutic for autism. To determine what might contribute to response susceptibility, we treated the 16p11.2 deficiency and FMR1 knockout mouse models with intranasal oxytocin. Methods: Intranasal oxytocin was administered once a day, for 28 days, starting at 5 weeks of age. During the third week of treatment, the behaviour of the mice was assessed in multiple domains, including sociability and repetitive behaviours. The mice underwent in vivo and ex vivo neuroimaging throughout various points in the study. Results: Treatment had no significant effect on neuroanatomy and, for the most part, did not enhance the behaviours of either mouse model, though it slightly increased social behaviours in the 16p11.2 mouse. Discussion: Neither model showed a treatment effect in their neuroanatomy, and very little effect on behaviour. This indicates that oxytocin may not be a good treatment option for either the 16p11.2 or FMR1 mutant mice, and therefore humans with the 16p11.2 mutation and children with Fragile X Syndrome. Future directions involve looking at the response of multiple strains of autism-related mouse models to several promising therapeutics used in human patients with autism, yielding the ability to establish a translational paradigm for predicting responders from non-responders.

1-F-140 Automatic detection of the slow waves in non-anaesthetised mice: comparison of traditional and novel methods

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Slow waves (SW) are electrographic events dominating in EEG during SW sleep that are mediated by synchronous behavior of a large number of neurons. Estimation of their number and other features may improve evaluation of normal SW sleep and pathological EEG activity. The SW can be easily identified by visual inspection, but available methods of their automatic detection are not robust. Here we present comparison of SW detection results obtained with the newly proposed machine-learning neural network (NN) method and traditional threshold-based methods in LFP recordings from frontal cortex of C57/BL6 mice. The distribution of amplitude, duration and fast frequency (FF) activity of depth-positive waves in non-anaesthetized mice indirectly suggested some thresholds for the detection of SWs. Large SWs were detected in agreement of each of the 4 methods. NN method detected SWs from which 4.7% were not identified by any other methods, but had a shape of smaller SWs. NN confirmed 95.6% of events found by 3 other methods that reflects the low level of false negative results. Amplitude and duration thresholds had higher detection rates, they found 96.6% and 99% of SWs, correspondingly, that were

found with 3 other methods. However, 12.1% and 41.3%, of SWs found with these methods were not confirmed by any other method. FF activity showed the lowest level of correct detection. We conclude that NN approach alone has better quality of automatic SW detection appropriate for on-line use, but combination of all methods improves the overall quality of results. Supported by CIHR and NSERC.

1-F-141 Comparing effects of alcohol and marijuana: A go/nogo fMRI study in young adults

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Alcohol and marijuana are the most frequently used drugs by adolescents. Further understanding of the effects of these drugs, particularly marijuana, on the adolescent brain is important as an imminent shift in accessibility is on the horizon. Perceived risk and normalization of use will inevitably be altered. The present study compared the effects of alcohol to those of marijuana, on a fMRI Go/No Go task, in adolescent users.17 alcohol users were compared with 11 non-users, and 10 marijuana users were compared with 14 non-marijuana users using whole brain BOLD fMRI on a 1.5T Siemens scanner. Drug using groups were compared to their respective control groups. No significant differences in performance were found between groups. fMRI analyses revealed significantly more activity in both drug groups compared to controls, but the areas of increased activity during the response inhibition were different for the two drugs. Alcohol users had significantly more activation in the left dorsolateral prefrontal cortex than controls. Comparatively, the marijuana group showed significantly more activation in the somatosensory cortex, and the premotor area and were located bilaterally, suggesting effects spread more diffusely across the brain. These results show that in addition to an effect of marijuana and alcohol on neural mechanisms, these effects seem to manifest differently in the adolescent brain. Of particular concern is what might be a synergistic effect of using both drugs, as these results suggest even greater widespread effects across the brain.

1-F-142 The Effects of Early Life Trauma on the Self in Eating Disorders

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Introduction: Eating disorders (EDs) are a category of mental illness defined by irregular patterns of food consumption. Negative early life events (e.g., abuse and parental neglect) may alter brain resting-state activity and impair internal perceptions (i.e. interoception) (Eshkevari et al., 2014; Philip et al., 2013; Wiebking et al. 2015), which can trigger the onset of an ED. Objectives: Assess (1) the impact of early life events on the self and interoception in EDs, and (2) assess changes in interoception following ED treatment. Method: Participants will be 50 individuals with EDs versus 50 healthy participants. Participants will complete scales on trauma, depression, and body image. Participants will also engage in tasks to assess time perception and interoception. All measures will be administered one and 10 weeks after the start of treatment for participants with EDs. Control participants will only be assessed at one time point. Hypotheses: Compared to a control group, individuals with EDs (a) are more likely to have suffered from early-life trauma and will exhibit a distorted perception of the self and time; (b) will judge time as moving more slowly; and (c) exhibit improvements in perception following 10 weeks of treatment. Implications: Understanding how patients with EDs perceive external and internal cues related to self and time will inform how these variables affect ED symptoms and treatment. This study will form the basis for future investigations that will use brain scan technology to identify abnormal resting state activity in patients with EDs.

1-F-143 Utilization of Loss- and Gain- of- Function Approaches to test the Functional Role of Progenitor Cells in Stroke Recovery

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Pre-clinical rodent and post-mortem human studies have identified an increase in proliferation and ectopic migration of stem/progenitor cells (PCs) to the stroke. Yet, four loss-of-function studies have conflicting findings on whether the ablation of PCs impedes motor and/or cognitive function post-stroke. This study uses loss- and gain-of-function approach to examine the role of PCs in stroke recovery. The transgenic GFAP-TK rat model was used for the inducible ablation of PCs prior to induction of stroke using Endothelin-1. The inducible Bax knockout (iBax) mouse was used to promote PC survival following induction of stroke using the photothrombosis model. The PCs response to stroke and long-term sensory-motor recovery and cognitive function was measured post-stroke. The GFAP-TK rats had an almost complete ablation of PCs in the absence of any changes in infarct size, or motor and cognitive recovery compared to controls. The iBax mouse had a striking ~5 fold increase in PCs around the infarct, and in the dentate gyrus. However, there were no differences in sensory-motor function, spatial learning and memory, or infarct size in the iBax versus WT mice. These results contradict the loss-of-function models, which may be attributed to differences in ablation and stroke models. Our findings suggest that PCs are not required for recovery and that increasing PC survival is insufficient to improve stroke recovery.

1-F-144 Mice with deletion of choline acetyltransferase in VGLUT3-positive neurons present memory deficits and altered social behaviour

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As part of the glutamatergic system, vesicular glutamate transporter 3 (VGLUT3) can be found within cholinergic neurons which use choline acetyltransferase (ChAT) to produce acetylcholine (ACh). We intend on testing the behavioural impact of loss of ChAT within neurons that co-express VGLUT3. Based on past experiments assessing the impact of loss of cholinergic activity on social memory, we hypothesize that mice unable to synthesize ACh in VGLUT3-positive neurons will present sociability and social memory deficits. All experiments were conducted on male mice. We used an open-field locomotion test to measure animal activity, and Morris Water Maze to measure spatial memory. We also conducted social preference and social memory tests. Our results indicate that mice with reduced/absent cholinergic tone from VGLUT3-positive neurons show deficits in social memory and decreased sociability. Additionally, these ChAT knockout mice are hyperactive and show deficits in spatial memory measured using the Morris Water Maze. These results suggest that reduced cholinergic tone from VGLUT3-positive neurons regulate social interactions, a critical feature in neuropsychiatric diseases, including autism-spectrum disorders. Cholinergic neurons containing VGLUT3 during development and adulthood are present in the striatum and basal forebrain, suggesting a critical role for these neurons in sociability. These mice may help to model some of the critical cognitive deficits in neuropsychiatric disorders.

1-F-145 Neural correlates of trial-to-trial adjustments of speed-accuracy trade-offs in premotor and primary motor cortex

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Recent studies have shown that animals adjust the speed-accuracy trade-off (SAT) of their decisions by modulating the baseline and gain of choice-related activity in sensorimotor regions. Here, we show how this adjustment occurs between individual trials within a given SAT context. Two monkeys performed a reach decision task in which probabilistic sensory evidence evolved over the course of each trial and the guess could be made at any time. We found that in dorsal premotor cortex (PMd), about 16% of cells had significantly stronger baseline activity after correct than error trials. This effect was consistent across different SAT contexts and for many cells, persisted during deliberation. Because cells exhibiting this effect also tend to be implicated in the deliberation process and amplified in fast SAT conditions, the post-success increase in their activity may be responsible for the small but significant behavioral tendency for guesses to be hastier after correct trials, especially in fast SAT conditions. About 14% of PMd cells showed significantly stronger baseline activity after errors. These cells were less related to deliberation and may be involved in withholding actions. We found similar effects in M1, with about 18% of cells showing stronger activity after correct trials and 26% after errors, with both groups more related to movement than deliberation. These data suggest that SAT policies are defined by the parameters of the competition between action choices, which are adjusted using the recent history of reinforcement.

1-F-146 Nicotinic restoration of GABAergic transmission in prefrontal cortex mediates facilitative effects on multisensory integration deficits in rodent models of schizophrenia

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Schizophrenia is associated with atypical multisensory integration. We have developed a rodent multisensory oddity paradigm (MSO), which enables testing of binding abilities across multiple modalities (tactile-visual & olfactory-visual). This study assessed the ameliorative effect of nicotinic acetylcholine receptors (nAChR) and their interaction with the GABAergic system in the prefrontal cortex of ketamine-treated rats performing the MSO tasks. Rats were sub-chronically treated with the NMDA receptor antagonist ketamine or saline. Ketamine-treated rats were selectively impaired on the tactile-visual and olfactory-visual MSO tasks. Intra-orbitofrontal cortex (OFC) nicotine or α4β2 nAChR agonist ABT-418 administration reversed the MSO impairment; this facilitation was blocked by systemic co-administration of the GABAA antagonist bicuculline. Whole-cell electrophysiology revealed decreased GABAergic currents in the OFC of ketamine-treated rats, and these were normalized by activation of α4β2 nAChRs. Moreover, parvalbumin (PV)-immunoreactivity was decreased in the OFC of ketamine-treated rats. Pharmacogenetic inhibition of PV interneurons (PVINs) in the OFC of PV-Cre mice using DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) selectively impaired tactile-visual MSO task performance; this deficit was reversed by systemic administration of ABT-418. These results suggest that α4β2 nAChR activation of the GABAergic system, specifically PVINs, in the OFC underlies the remediation of a robust multisensory binding impairment in ketamine-treated rats.

1-F-147 Electrophysiological correlates of subphonemic processing in spoken word recognition

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In natural speech, a single phoneme may have a number of different acoustic-phonetic realizations as a result of coarticulation, or overlap between articulatory gestures. While models of spoken word recognition differ in the role accorded to this subphonemic information, previous research has indicated that coarticulatory mismatches affect both behavioural and electrophysiological responses. In this electroencephalography (EEG) study, we presented listeners with words in which the initial consonant phoneme had been spliced so that its subphonemic acoustic properties either matched or mismatched the following vowel. The subphonemic cues in the mismatched onsets differed from the spliced vowel in height, backness, or both. We found an effect of congruence not only on the Phonological Mapping Negativity (PMN), present between approximately 230-350ms, but also on the N100, an earlier component previously thought to be modulated only by acoustic properties of an auditory stimulus. Furthermore, both components were affected by the type of incongruity. These results suggest that the PMN, commonly believed to be elicited by unexpected events at the phonemic level, is also sensitive to acoustic-phonetic mismatches, and that the N100 reflects processing not just of physical properties of the acoustic signal, but also of fine-grained subphonemic information.

1-F-148 ERP investigation of attentional and language processes after concussion

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It has been demonstrated repeatedly that mild traumatic brain injury (mTBI) (concussion) results in neurological deficits (Covassin et al., 2008; Karr et al., 2014). Cognitive neuroscientists have shown that individuals suffering from a concussion show an impediment in the cognitive processes associated with attention and language (Dupuis et al., 2000; Karr, et al., 2014). We implemented a series of event-related potential (ERP) experiments to investigate the electrophysiological differences between clinically-diagnosed concussed adolescents (CA) and healthy control (HC) participants. A paradigm was developed that examined three separate cognitive tasks. In Task 1, attentional processes were examined using a P3b auditory oddball paradigm. In Task 2, semantic-related language processes were evaluated using an N400 auditory sentence comprehension task. In Task 3, cognitive processes associated with the recognition of deviant tones, that a participant was not consciously attending to, were assessed using the mismatch negativity (MMN) component. Preliminary results show significantly smaller ERP amplitudes in the CA than HC participants across all three tasks ($p<0.05$). Our work provides evidence to suggest that a concussion results in an altered state of brain electrophysiology that consequently affects cognitive processing associated with both language and attention. While this study demonstrates that a concussion leads to attention and language deficits, the main focus of our work is to develop tools to identify when an individual can safely return to physical activity.

1-F-149 Characterizing Eye-movement Behaviour and Kinematics of Non-Human Primates in a Virtual Environment

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Virtual environments have become a popular way of studying cognition in humans, but only have limited documentation and behavioural characterization in non-human primates. In order to characterize eye

movements in non-human primates navigating a virtual environment, two male rhesus macaques performed a context-object associative learning task and a foraging task within a virtual environment, as well as a classical visually guided saccade task. We recorded eye positions to characterize their eye movements, and investigated the effects of different tasks, and task demands, on oculomotor behaviour.We classified saccades, intersaccadic intervals as either fixations or smooth pursuits, and post-saccadic oscillations. We characterized the amount of time spent on each behaviour, and compared the durations of the intersaccadic intervals across each task. We found similar results between the virtual environment tasks, but both were different from the visually guided saccade task, with far more smooth pursuit movements in the virtual environment. When breaking up the context learning task into different task periods, there were significant changes in the duration of intersaccadic intervals.When comparing the saccadic main sequence, we did not find any differences between the three tasks. After examining the task periods in the context learning task, we found that task period had an affect on the main sequence. This work extends eye-movement behaviour studies into in an expanding paradigm, and also shows that the kinematics can change based on task demands over the course of a trial.

1-F-150 Disturbed Object Processing in 3xTG and 5xFAD Mouse Models of Alzheimer's Disease: Going Beyond "Object Recognition"

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Object recognition assess declarative-like memory in rodents and is sensitive to cognitive deficits in mouse models of Alzheimer's disease (AD). Object recognition, however, is not a unitary process, and there are many uncharacterized facets of object processing that have relevance to AD. To clarify the nature of object processing deficits in AD models, we are systematically evaluating performance on various tasks designed to require processing of different types of information about objects: object identity (i.e., object recognition per se; OR), spatial processing (object location; OL), temporal processing (object recency), and multisensory integration (cross-modal object recognition and multisensory object oddity; MSO) in 12-month-old 3xTG and 5xFAD mice. 3xTG males were impaired on OR when the retention delay was 5min or 3h, whereas females were selectively impaired at 3h. When spatial cues were minimized, using a modified Y-apparatus, both 3xTG males and females had intact OR at 5min. Conversely, 5xFAD males and females were impaired on OR at 5min and 3h regardless of spatial cues. Preliminary results also show impaired OL at 5min and 3h in 3xTG males, females and 5xFAD females; impaired object recency in 3xTG females; and impaired MSO in 3xTG males, females and 5xFAD females. By performing a cross-strain analysis of object processing with tasks that are dependent on not entirely overlapping neural mechanisms we should be able to better characterize the multi-faceted nature of object processing deficits and their relation to specific elements of AD pathology.

1-F-151 Phosphorylation of Glucocorticoid Receptor in Hippocampal Neurons of Rats Trained in Inhibitory Avoidance

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Stress induces the release of corticosterone (CORT) in rodents and cortisol in humans. CORT reaches the glucocorticoid receptor (GR) in the brain where GR is phosphorylated at serine 211 (pGRser211) and

internalized into the nucleus, acting as a transcription factor. The GR is present in a high concentration in CA1 and dentate gyrus (DG) of the hippocampus, with a smaller proportion in CA3. These regions are involved in memory consolidation of inhibitory avoidance (IA), where an electric foot-shock is associated with a context. We quantified nuclear pGRser211 in CA1, CA3, and DG of rats trained in IA, using different foot-shock intensities (0.5, 1.0, and 2.0 mA); we also studied three control groups: the first one was placed in the context but without foot-shock (0.0 mA), the second received only the foot-shock (2.0 mA) without training, and the last one was a home-cage group. Brains were disected 60 min after training and cryosectioned for immunodetection of pGRser211+ cells. We found a higher retention in the groups trained with 1.0 and 2.0 mA than in the 0.0 mA or 0.5 mA groups. The highest proportion of pGRser211 cells was found in CA1 of the 2.0 mA trained group. No changes were observed in CA3 and DG. These findings suggest that activation of GR in CA1 is involved in the consolidation of a stronger memory of IA, possibly through the modulation of gene expression. We thank Norma Serafín, Cristina Medina, Leonor Casanova, Nydia Hernández and Martín García for technical assistance. Supported by PAPIIT-UNAM (IN202414) and CONACyT scholarship 621351/331018.

1-F-152 Differential effects of the T-type calcium channel antagonist, Z944, on behaviours associated with morphine and amphetamine addiction

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Mixed L-/T-type calcium channel antagonists attenuate morphine-induced conditioned place preference (CPP), and amphetamine-induced CPP. Subtype specific antagonists for T-type calcium channels attenuate nicotine-reinforced behaviours in rats. Here we investigate the effects of a novel T-type calcium channel antagonist, Z944, on the acquisition and expression of morphine and amphetamine CPP. Furthermore, we examine Z944 for aversive or reinforcing properties, and determined changes in locomotion with Z944 alone and in conjunction with morphine. CPP was induced with either morphine (5mg/kg, IP) or amphetamine (1.5mg/kg, IP) and Z944 (vehicle, 5, 7.5mg/kg, IP) was administered 15 min prior to conditioning sessions for acquisition experiments. For expression experiments, Z944 was administered prior to the test session. Aversive and reinforcing properties of Z944 were evaluated using a CPP/ CPA procedure. Effects of Z944 on locomotor activity were tested alone or in conjunction with morphine. Z944 dose-dependently attenuated the acquisition of morphine CPP and expression of amphetamine CPP. Further, Z944 alone had no inherent reinforcing or aversive effects, despite causing a decrease in spontaneous locomotor activity. It was also revealed that Z944 enhanced morphine-induced hypolocomotion. Ongoing experiments will examine combined amphetamine and Z944 on locomotor activity. These results suggest that T-type calcium channel antagonists differentially attenuate behaviours reinforced by several classes of drugs of abuse.

1-F-153 Brain circuits involved in cross-modal target selection for gaze-shift

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Consider a subject who is presented with two stimuli, with no emotional or semantic significance, though with possibly variable spatial and / or temporal features, from different modalities, and asked for spatial localization. The subject, first, needs to infer whether the stimuli belong to same or separate events based on the spatiotemporal features of the stimuli. The subject localizes an optimally integrated position based on the two spatial position information in case of inference of a unique cause, and

localizes the more salient of the two events in case of inference of separate causes. In a previous study we proposed a model for solving the causal inference problem and the question of where to shift the attention, namely by making a gaze-shift. Here we extend that model and suggest a mechanism, within the decision making framework introduced before, which answers the question of when to make a gaze-shift. We propose a computational measure of confidence on the winning plan as a criterion for sending the plan to be executed. We propose a model for reaction time variability considering, for the first time, both spatial and temporal factors. We produce simulations that validate our model by comparing its results with trends observed in experiments where subjects were asked to make gaze-shifts towards cross-modal stimuli presented with systematically changing spatial and temporal disparities. We also extend the status que by providing predictive simulations for situations where the reliabilities of the stimuli change in both cross-modal and unimodal situations. We final

1-F-154 Effect of steady-state methadone exposure on hedonic reactivity and caloric intake in rats

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Central opioid systems regulate hedonic responses to natural rewards. What is less clear, however, is how these responses are modified in the context of chronic, steady-state, activation of mu-opioid receptors characteristic of maintenance on agonist drugs such as methadone.To explore this question, male Sprague-Dawley rats were given unlimited home cage access to a highly palatable solution (50% high fructose corn syrup; HFCS), in addition to standard rat chow and water. They were then surgically implanted with osmotic mini-pumps releasing 0, 10 or 30 mg/kg/day methadone. During the 13 days of drug treatment, HFCS and chow intake were measured, in addition to locomotion assessed in activity chambers.Steady-state methadone exposure dose-dependently reduced total caloric intake, and this was associated with decreases in body-weight. Importantly, however, the percentage of caloric intake derived from HFCS was significantly increased by both 10 and 30 mg/kg/day methadone. It is unlikely that these effects on HFCS and chow consumption were due to impaired locomotion because activity levels were not significantly different between treatment groups.These data in rats indicate that chronic methadone exposure increases preference for highly palatable food, possibly because of increased hedonic reactivity. This finding in rats is consistent with the observation of elevated preference for sugar in methadone maintained subjects, and can perhaps explain the increase in body mass index that is observed following initiation of methadone treatment in opioid dependent subjects.

1-F-155 Role for striatal NFκB in neuroinflammation and depressive-like behaviours induced by saturated high-fat feeding.

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A bilateral relationship exists between obesity and depression. Diet-induced obesity (DIO), as the result of prolonged overnutrition, is characterized by low-grade inflammation from which the brain is not exempt. Inflammation is suggested to partake in depressive symptoms, notably in areas of the limbic system. We have shown, in mice, that DIO promotes depressive-like behaviours and neural adaptations in the nucleus accumbens (NAc). Recently, we found a saturated high-fat diet (HFD) results in depressive-like behaviours and NAc inflammation - including activation of the nuclear factor kappa-B

(NFkB) pathway. As NFkB is involved in both DIO and vulnerability to a depressive phenotype, we hypothesize HFD promotes depressive-like behaviours via NFkB in the NAc. Objective: Determine the role of NAc NFkB in HFD-induced depressive-like behaviours. Methods: C57Bl6 male mice fed a low-fat diet (LFD) or HFD were injected with an adenovirus delivering a dominant negative inhibitor of kappa-B kinase-beta (IKKBdn) - an upstream molecule of NFkB - or green fluorescent protein (GFP) into the NAc. We assessed anxiety and depressive-like behaviours with the elevated-plus maze, marble burying and forced swim tests. Inflammatory makers in the NAc were measured by qPCR. Results: IKKBdn reverses the behavioural deficits induced by HFD. Brain tissue analysis also confirms a reduction of inflammation. Conclusion: NAc NFkB activity mediates inflammation and depressive-like behaviours induced by HFD. These results reflect the prevalence of depressive symptoms among obese individuals.

1-F-156 Effect of developmental lesioning of prefrontal cortex on attentional set-shifting in rats

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Partial ablation of subplate neurons of the developing prefrontal cortex (PFC) in neonatal rat pups results in the adult emergence of positive and negative symptom-like features and structural abnormalities that are consistent with schizophrenia. Within the PFC, these changes include 1) altered laminar distribution of parvalbumin immunoreactive neurons, as well as thalamo-cortical and dopamine fibers; 2) decreased synaptophysin immunolabeling, and; 3) loss of GABA transporter-1 immunoreactivity restricted to upper lamina of the PFC. As glutamate, dopamine and GABA neurotransmitters play important role in executive functioning, we hypothesized that subplate lesioned rats will show executive function deficits. Neonatally-lesioned and sham-operated (control) groups of animals at 14-20 weeks of age underwent an operant condition-based attentional set-shifting task. Set-shifting task requires rats to learn visual-cue discrimination (press the lever associated with the visual cue light), and then, shift to the response discrimination strategy (always press an assigned lever regardless of visual cue light) to obtain reinforcer (sucrose pellets). Preliminary results showed that the average number of trials required by the lesioned group to achieve the performance criterion was greater than average number of trials taken by the control group, but this difference was not statistically significant.

1-F-157 Hook, worm, and noodle: Parsing perceptual and conceptual processes of the medial temporal lobe

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How does the brain represent relationships between meaningfully associated real-world objects? The answer to this question is complicated by the close relationship between semantic and perceptual similarity: meaningfully related objects (e.g. a tiger and a lion) often share many visual features (e.g. sharp teeth, claws, and forward-facing ears). A number of separate investigations have highlighted the medial temporal lobe (MTL), and particularly the perirhinal cortex (PRC), as sensitive to both the semantic and perceptual similarity between objects. We therefore developed a novel stimulus set and corresponding forced-choice task to disentangle these interrelated roles of the PRC. In this task, participants matched a target word ("worm") to a correspondent semantic ("hook") or perceptual ("noodle") match, both presented amongst foils. Crucially, items were selected such that the semantic

match shared minimal perceptual features with the target object, and vice versa. We compared task performance of amnesiac patients with and without PRC damage to age- and education- matched controls. Despite the experimental separation of perceptual and semantic relatedness, PRC damage was associated with impaired performance on both the semantic and perceptual match tasks, whereas patients whose damage excluded the PRC showed normal performance on both tasks. Our findings implicate the PRC in both perceptual and semantic representations of objects, even when the overlap between these dimensions is experimentally controlled.

1-F-158 Differential implication of sleep stages in procedural memory consolidation following a daytime nap: a comparison between meditators and non-meditators.

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Introduction: Recent research suggests that rapid eye movement (REM) sleep and non-REM (NREM) sleep are both involved in processes of procedural memory consolidation. In addition, the practice of meditation has been shown to increase brain plasticity and affect sleep and memory. This study explores the potential roles of REM and NREM sleep in procedural memory consolidation following a daytime nap in Vipassana meditators (MED) and non-meditating controls (CTL). Methods: 22 MED participants (age= 25.8±4.1; f = 11); and 20 CTL participants (age= 25.0±4.8; f=10) performed a procedural memory task (Wii Fit), measuring postural stability before and after a daytime nap. Postural stability was measured by the time spent balanced on the Wii board during the task; task performance was calculated by the Wii program. Sleep was measured with polysomnography. Results: There was a positive correlation between time spent in REM sleep and increase in time spent while balanced ($r=.509$, $p<0.001$) and task improvement ($r=.407$, $p<0.007$) in CTL, but not in MED. In contrast, there were positive correlations between time spent in NREM stage2 and increase in time spent balanced ($r=.432$, $p<0.045$) and task improvement ($r=.372$, $p=0.088$) in MED, but not in CTL. Discussion: Improvement on a procedural memory task may involve different mechanisms of sleep-dependent memory consolidation as a function of past experience with bodily-focused meditation such as Vipassana. Meditation may activate neuroplasticity-related strategies for balance learning associated with NREM rather than REM sleep processes.

1-F-159 Building informative neural ensembles to decode attention in primate lateral prefrontal cortex

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The allocation of attention can be decoded from the activity of lateral prefrontal cortex (lPFC) neuronal ensembles. One issue that remains unclear is the impact of a neural ensemble's size and composition on decoding attention. To investigate this, we recorded the responses of neurons in lPFC of two macaques via microelectrode arrays as they performed a spatial attention task; the animals had to direct attention to a cued target positioned in one of four visual quadrants while ignoring 3 distractors positioned in the remaining quadrants. We systematically altered the size and composition of the neuronal ensembles to evaluate their information content using a linear decoder. We found that the location of spatial attention was reliably decoded from ensembles of approximately 50 units (mean accuracy 76%; $P<0.05$ Shuffle test). We then progressively increased the number of neurons in an ensemble and assessed

decoding performance using two methods: first, we built subnetworks comprised of the most informative neurons; second, we built subnetworks that maximized information of the ensemble. The decoding performance of the most informative subnetworks was higher than those composed of the most informative units. Interestingly, the most informative subnetworks were not comprised of most informative units (average 6% increase; $P<0.05$ Wilcoxon signed-rank test). These results indicate a complex effect of ensemble size and composition on the coding of attention in lPFC neuronal ensembles.

1-F-160 Synaptic zinc is required for the enhancement of adult hippocampal neurogenesis

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In adult hippocampal neurogenesis (AHN), newly formed cells migrate into the granule cell layer of the dentate gyrus where they express neuronal markers, elaborate axons, make functional synaptic connections, and improve hippocampal-dependent behaviours. The level of AHN can be modulated by a variety of factors-it is increased by exercise, environmental enrichment and exposure to selective serotonin reuptake inhibitors (SSRIs); and decreased by stress and ageing. Here, we examine whether synaptic zinc is essential for the modulation of AHN by environmental enrichment, SSRIs, and stress, in normal mice (ZnT3-wildtype, WT) compared to mice lacking synaptic zinc (ZnT3-knockout, KO). We found that environmental enrichment- and SSRI-induced increases in AHN, and consequent improvements in hippocampal-dependent behavioural tasks were ablated in ZnT3-KO mice. We also examined ZnT3-WT and -KO mice that were chronically exposed to fluoxetine, while in stressed or non-stressed conditions. We found that synaptic zinc is necessary for fluoxetine-induced increases in AHN, in both stressed and non-stressed mice, but not for stress-induced decreases in AHN. The behavioural benefits associated with increases in AHN were ablated in all stressed animals, regardless of genotype. In non-stressed animals, only WT animals showed any behavioural benefits of fluoxetine. These data implicate synaptic zinc as being essential for experience-dependent enhancement, acting upstream of the effects of environmental enrichment and fluoxetine, but is not involved in the stress-induced suppression of AHN.

1-F-161 Enhanced morphological development of adult generated neurons by optogenetic stimulation decreases memory stability.

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New neuron survival is activity dependent but it remains unclear how activity might influence the growth and development of individual immature neurons in the adult hippocampus. Here we asked whether structural modifications of immature neurons could be produced by brief but chronic optogenetic activation of new neurons. We infected dividing neurons in the dentate gyrus with a ChR2-GFP expressing retrovirus followed by stimulation of the labeled neurons for 14 days. We then waited an additional 14 days before examining the morphology of the infected neurons using CLARITY. We found that 2 weeks of stimulation produced a robust increase in the size and complexity of the new neurons including changes in spine density and large mossy terminal volume. We have previously shown that increasing the number of new neurons after learning will decrease the persistence of that memory. (Akers et al.,2007). This effect is likely due to the interfering effect of new neurons integrating into the

existing circuitry. Therefore, we next asked whether the structural modifications produced by chronic optogenetic stimulation were sufficient to produce this behavioural phenotype. We infected mice with a ChR2-GFP retrovirus, performed fear conditioning and stimulated the infected neurons as before. When we tested the mice for fear memory one month after training we found that mice that received stimulation showed impaired memory retention despite no change in the number of new neurons. The altered morphology of a small number of new neurons is sufficient to reduce memory stability.

1-F-162 Polyunsaturated Fatty Acids And Their Metabolites As Possible Mediators Of Depression-Like Behaviors In Rats

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An imbalanced ratio of dietary Omega-6(n-6)/Omega-3(n-3) polyunsaturated fatty acids(PUFAs) contributes to onset and severity of depression-related disorders; however the molecular mechanisms involved remain unclear. We hypothesize that the ratio of dietary PUFAs determines hedonic responses and associated biomarkers. Rats fed a control, n-3- or n-6-rich diet were sacrificed and brains were collected for phospholipid composition(gas chromatography) and eicosanoid analysis(liquid chromatography) in the pre-frontal cortex(PFC), hippocampus and hypothalamus. Another cohort of rats, in the same dietary condition, was tested for anhedonia-like behavior, using a sweet solution preference test. We found that PUFA composition of brain membrane reflects the diet: there are higher concentrations of n-3 PUFAs on membrane phospholipids of n-3-fed rats; and higher concentrations of n-6 PUFAs on membrane phospholipids of n-6-fed rats. Brain regional heterogeneity in the patterns of eicosanoid elaboration was observed after intake of the above-mentioned diets: there are higher amounts of these fatty acids metabolites in the PFC, compared to the hypothalamus and hippocampus. Moreover, exposure to n-6-rich diet reduces sweet solution consumption, suggestive of anhedonic behavior.A dietary imbalance of n-6/n-3 modulates anhedonia, brain phospholipid composition and the production eicosanoids, which regulate several processes within the brain, including mood.Our results will provide valuable information on the involvement of nutrient-derived signals as potential biomarkers of depression.

1-F-163 Does Physical Activity prevent Dementia? A systematic review

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Context: Dementia is a prevalent disorder in the aging population, and decreases the quality of life of individuals and their caregivers. Given pharmacological strategies can treat the symptoms but not the cause of dementia, more research is needed to identify factors that could prevent it. The aim of this review is to examine whether physical activity (PA) could be protective against the onset of dementia. Method: A search was conducted up until June 2015 on PubMed and PsyInfo databases building on a previous systematic review (Blondell et al., 2014). Studies were included if they were of prospective design; included a population-based sample; with a dementia assessment description; with PA assessed at baseline; and with participants aged ≥ 40 years. A total of 24 studies were included. The majority of the studies (n=19) reported a significant negative association between PA and dementia. PA showed a stronger effect on Alzheimer's disease compared to other types of dementia. Although it is difficult to identify an optimal dose of PA, most studies (n=13) showed that higher levels of PA have a stronger protective effect when compared to lower levels. Nevertheless, even less than 150 minutes per week of

PA appears to be protective. Conclusion: There is consistent evidence that PA is associated with a reduced risk of dementia. There is no clear evidence of an optimal dose but common guidelines for PA appear an appropriate recommendation. Keywords: Dementia; Physical Activity; Alzheimer
Acknowledge: CNPq (process # 202987/2014-0)

1-F-164 Using pupil response to assess cognitive function across the healthy lifespan

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Decline in cognitive functions occurs as a result of natural aging, but aging is also associated with neurological disorders. An easy-to-measure method that is increasingly used in clinical investigations to assess cognitive function is pupillometry measurement. Neurophysiological experiments have shown that pupil size is controlled by converging inputs from both bottom-up sensory and top-down cognitive signals. To study neurological disorders at different stages of disease progression, changes in pupil dynamics due to aging need to be understood in order to delineate normal ageing from clinical neural degeneration. Here, we examined pupil dynamics in different ages and hypothesized that components of the pupil response modulated by cognitive signals should weaken with increased age as a result of cognitive decline with natural aging. Pupil size was recorded in healthy subjects (age 17-80) while performing the interleaved pro- and anti-saccade task. Subjects were instructed via the colour of a fixation cue to generate either an automatic eye movement toward a peripheral stimulus (pro-saccade) or a voluntary eye movement in the opposite direction (anti-saccade). The pupil constricted shortly after the presentation of a fixation cue following by pupil dilation. Moreover, there were age-related trends in the pupil response. The results demonstrated changes in pupil dynamics as a result of aging, providing the baseline with which abnormal pupil responses due to neurological deficits can be studied.

1-F-165 Using eye movements to establish distinct biomarkers across the healthy lifespan

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As the brain ages, cognitive abilities such as executive function and memory decline. In order to differentiate neurodegenerative disorders from normal aging as early as possible, cognitive decline due to normal 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 interleaved pro- and anti-saccade task (IPAST) and a free viewing (FV) paradigm in subjects aged 17-80 years. The IPAST requires subjects to generate anti-saccades (voluntary eye movement away from stimulus) or pro-saccades (automatic eye movement toward stimulus) depending upon an on-screen colour instruction. IPAST requires that subjects dynamically update goal-directed objectives on a trial-by-trial basis, amplifying the effects of any underlying cognitive dysfunction. The FV paradigm involves subjects observing video clips with differing semantic content to assess basic saccadic abilities. Subjects over 60 had significantly more direction errors, increased reaction times, and increased latencies to initiate anti-saccades. Compared to pro-saccades, which were stable across all ages, anti-saccades were significantly affected as age increased. These results provide insight into normal cognitive ability and changes that take place across the healthy lifespan, providing a baseline to evaluate saccade deficits and abnormalities caused by neurological disorders.

G- Novel Methods and Technology Development

1-G-166 Novel formulation using dendrimers for the intranasal drug delivery to brain

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Brain neurotherapeutic delivery is challenging because of stringent properties of the blood brain barrier, preventing entry of most small hydrophilic and almost all large molecules from blood circulation. Brain accessibility from the nasal cavity through the olfactory route presents a possibility for targeting these drugs but is limited in most novel neurotherapeutics due to inadequate aqueous solubility. In the present study, we investigated using PAMAM dendrimers to enhance solubility of four water insoluble drugs (lurasidone, resveratrol, curcumin and haloperidol) and investigated potential of such solubility enhancement on brain targeting of haloperidol following intranasal administration. Dendrimers enhanced resveratrol and haloperidol solubility, decreased lurasidone and did not largely affect curcumin. Drug solubility was further enhanced with polysorbate 20 and ethanol. Haloperidol formulation prepared with dendrimers, polysorbate 20 and ethanol was administered to rats through oral, nasal and intraperitoneal route, tested for catalepsy and locomotor suppression. Haloperidol formulation, when administered intranasally induced similar locomotor suppression but superior cataleptic response than those induced by oral or intraperitoneal administration of the same formulation as well as intraperitoneal administration of a positive haloperidol control. This study proves dendrimer and nasal route potential for drug to brain targeting with non-invasive administration as well as possibly alleviating systemic side effects associated with oral or parenteral administration.

1-G-167 An axicon-based light sheet microscope for large scale and high resolution brain imaging

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Laser scanning microscopy allows visualizing the very complex circuitry of the brain with high resolution. However, imaging the entire brain is challenging because of its relative opacity to light. In addition, laser scanning microscopy systems are time-consuming. We present an approach combining optical clearing and two-photon fluorescence light sheet microscopy to obtain whole brain images in record time with high resolution. In a previous study, we were the first to use an axicon to extend the depth of field of a two-photon microscope. We are able to generate two-photon fluorescence over a thin long line with constant thickness. More importantly, we are able to increase the depth of field without resolution reduction. This property is very useful in our light sheet microscope since, we are able to have a large field of view without compromising the axial resolution. Producing light lines with sufficient energy remains challenging since the emission of two-photon fluorescence is a function of the square power of the excitation laser. For that reason, we use a regenerative-amplifier laser, which produces femtosecond pulses with 320 times more photons compared to standard pulsed lasers used in two-photon microscopy. Our combination of these technologies promises to transform our ability to understand the neuro-circuitry of the brain and thus significantly advance the understanding of neurological diseases which involve remodelling of brain connections.

1-G-168 Zero-Mode Waveguide Technology for Fluorescent Single-Subunit Counting

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A major challenge in studying plasma-membrane bound proteins has been to elucidate their subunit stoichiometry. Recently, we have successfully implemented an automated fluorescent single-subunit counting technique to accurately determine the stoichiometry of protein complexes expressed in mammalian cells (McGuire et al., 2012). Although this method has been invaluable in providing insight into protein stoichiometry, it has some important limitations. First, the penetration depth of fluorescence excitation using TIRF microscopy is not restricted to the plasma membrane, implying that the collected fluorescence signal also encompasses proteins contained within the intracellular space. This generates an appreciable background fluorescence that reduces the signal to noise ratio (SNR) of the system and restricts the ability to detect photobleaching steps. Second, stoichiometric measurements have been limited to using surrogate expression systems (e.g. HEK293 cells) rather than studying proteins in native environments. To address these issues, we have fabricated zero-mode waveguide nanostructures to further extend the abilities of the single-subunit counting methodology. The small size of the waveguide serves to isolate fluorescence illumination to single receptor complexes, even from areas with high expression density, and provides an effective means of significantly increasing the SNR of the system.

1-G-169 Using Induced Pluripotent Stem Cells to Model Rare Neurodevelopmental Disorders

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The development of accurate and informative models is essential to the investigation of any disease. Rare neurodevelopmental disorders face immense challenges developing credible models, as the scarcity of subjects and the difficulty of obtaining human neural cells have limited the resources available to researchers. However, many of the challenges that have stymied models of rare neurodevelopmental disorders have been significantly reduced due to recent advances in cell culture and genome editing. Here we present novel, optimized methodologies for modelling rare developmental diseases of the nervous system in vitro. We have developed a more rapid protocol through which primary fibroblasts can be converted to induced pluripotent stem cells (IPSCs) using a episomal vector and differentiated into neurons. The insertion of the episomal vector may be combined with the addition of a CRIPSR-Cas9 plasmid to enable simultaneous genome editing and IPSCs induction. Through optimization of the purification of IPSCs and the growth factors used to induce IPSC differentiation, fibroblasts were able to be successfully converted into either cortical or dopaminergic neurons within two months. This methodology represents a significant decrease in the time, effort, and cost required to model rare neurodevelopmental diseases in vitro. The research shown here demonstrates how researchers may develop neural disease models from terminally differentiated patient cells, or from healthy cells that are genomically edited to possess a disease-causing mutation.

1-G-170 Optogenetic control of cAMP and cGMP signalling in living neurons

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Second messengers, cAMP and cGMP, play an important role in intracellular signaling and are regulated through the rate of production by adenylyl cyclase(AC) and guanylyl cyclase(GC) and the rate of degradation by phosphodiesterase (PDEs). CAMP and cGMP have been implicated in synaptic plasticity and learning and memory through pharmacological and genetic manipulations. However given the rapid and dynamic signalling of cAMP and cGMP such manipulations fail to uncover their precise spatial and temporal roles. Optogenetic tools provide powerful methods to non-invasively control molecular activity in living neurons. To address the role of cAMP and cGMP signalling in synaptic plasticity, we previously utilized bacterial photoactivatable enzymes (AC, GC) to enhance signalling by light. To complement these optogenetic tools, we designed photoactivatable PDE4 and PDE5 to decrease cAMP or cGMP signalling independently. Such enzymes were created using a previously described method by fusing a phytochrome light sensitive domain to the catalytic domain of PDE2 (degrades cAMP and cGMP)(Moglich et al, 2014). Using this strategy and adjusting the fusion site between each domain we optimized the activity of PhPDE4, PhPDE5 in vitro. Upon milliseconds of illumination, PhPDE4 and PhPDE5 degrade only cAMP or cGMP, demonstrating their rapid photoactivation and catalytic specificity. Furthermore, they demonstrated a rapid inactivation upon removal of light. Together with photoactivatable cyclase (AC, GC), these tools will enable us to precisely control cAMP and cGMP signaling in living neurons.

1-G-171 Anesthetic Detection of Covert Consciousness in a Patient with Unresponsive Wakefulness Syndrome

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Introduction. Individuals who are behaviourally unresponsive are at risk of suffering from "covert consciousness". Recently, much attention has been given to using neurophysiological data to gain insight into the true level of consciousness of these patients. Previous studies have used functional and effective connectivity measures to assess consciousness, but results have been difficult to interpret due to the questionable comparison to healthy controls. Objective. To assess the level of consciousness of an individual diagnosed with Unresponsive Wakefulness Syndrome (UWS) using a "within-subject" test paradigm. Methods. A 29-year old male with UWS was presented with a half-hour auditory stimulation sequence while 64-channel EEG was recorded. The sequence was also presented while the individual was anesthetized, and upon recovery. EEG during baseline, anesthetized and recovery periods were analyzed for spectral composition, phase-amplitude coupling patterns, and functional and effective connectivity patterns. Results. While baseline EEG revealed pathological patterns, anesthesia induced changes in these patterns that are associated with loss of consciousness. Strength of functional connectivity decreased between centroparietal and centro-occipital regions, the direction of information flow became predominantly feed-forward, and network hubs shift to a frontal location. Conclusions. Using anesthesia to modulate the state of consciousness of unresponsive patients may be a viable method of assessing levels of consciousness.

1-G-172 Novel defined medium GAD-67-GFP-positive organotypic mouse spinal cord cultures; preservation of dorsal horn neuronal and astrocyte phenotypes

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Defined medium organotypic cultures (DMOTC) obtained from central nervous system slices preserve neural circuits for long-term in vitro studies. We have developed and validated spinal cord DMOTCs obtained from transgenic mouse embryos at days 12-13 of gestation that express green fluorescent protein (GFP) under the control of the glutamic acid decarboxylase (GAD-67) promoter marking inhibitory neurons. Glial fibrillary acidic protein (GFAP) and neuronal nuclei (NeuN) antibody immunostaining was done on chemically-fixed cultures, grown in vitro from 1 to 6 weeks after DMOTC generation. Whole-cell patch recording confirmed the presence of tonic, delay, irregular and phasic firing neurons in the dorsal horn, with 27% of recorded neurons (n = 50) expressing delay excitatory and 15% showing tonic inhibitory firing patterns. Of six GAD-GFP positive expressing neurons studied, 3 exhibited tonic, 2 phasic and 1 irregular firing patterns. This shows that the inhibitory phenotype is preserved in DMOTC of this species. Of 9 delay cells studied, none were GAD-67-GFP positive. These DMOTC show progressive increase in GFAP expression as indication of (astro) glia proliferation from week 1 to 3 whilst no further proliferation is seen afterwards. This suggests that excessive gliosis does not compromise the long term health of cultures. We have thus shown that mouse spinal cord DMOTCs show close similarities to rat spinal cord DMOTC and acute cord slices and as such provide a useful in vitro model to study cellular aspects of long term disease states.

1-G-173 Machine learning based framework for EEG/ERP analysis

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Event Related Potential (ERP) analysis of Electroencephalography (EEG) data has been widely used in research on language, cognition, and pathology. The high dimensionality (time x channel x condition) of a typical EEG/ERP dataset makes it a time-consuming prospect to properly analyze, explore, and validate knowledge without a particular restricted hypothesis. This study proposes an automated empirical greedy approach to the analysis process to datamine an EEG dataset for the location, robustness, and latency of ERPs, if any, present in a given dataset. We utilize Support Vector Machines (SVM) (Cortes & Vapnik, 1995), a well established machine learning model, with a feature selection algorithm named minimum redundancy maximum relevancy (mRMR) (Peng et al., 2005), on top of a preprocessing pipeline that produces a large bag of features including auto/cross power spectral densities, skewness, kurtosis, and electrode amplitudes. A hybrid of monte-carlo bootstrapping, cross-validation, and permutation tests is used to ensure the reproducibility of results. This framework serves to reduce researcher bias, time spent during analysis, and provide statistically sound results that are agnostic to dataset specifications including the ERPs in question. This method has been tested and validated on three different datasets with different ERPs (N100, Mismatch Negativity (MMN), Phonological Mapping Negativity (PMN), and P300). Results show statistical significance in the identification of all ERPs in their respective experimental conditions, latency, and location.

1-G-174 Ultrafast two-photon measurement of membrane potential using a genetically encoded voltage indicator

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Patch-clamp recordings are the gold standard for measurements of neuron electrical activity. However, patch-clamp recordings are less amenable to small neuronal compartments, as they are physically hard to access and rapidly deteriorate. Therefore, an optical method allowing subcellular measurement of

voltage in thick preparations would be desirable. To monitor voltage in multiple neuronal compartments, we combined random-access two-photon microscopy with the second-generation Accelerated Sensor of Action Potentials (ASAP2). First, ASAP2 could report action potentials (APs) under two-photon excitation with a ΔF/F of 14.1 ± 0.6% (n = 16). For a single trial at a scanning frequency of 925 Hz, ASAP2 reported APs with a signal to noise ratio twice larger than ASAP1 (ASAP2: 7.9 ± 0.5; ASAP1: 3.5 ± 0.2; P < 0.001). Furthermore, single-voxel detection of action potentials in single trial with ASAP2 was possible in almost all neurons tested (n = 15/16 neurons). Using two-photon excitation, ASAP2 detected APs at the cell body, in dendrites, dendritic spines, axons and axonal terminals. Finally, simultaneous multisite recording (28 to 41 voxels) at high-frequency (452 to 662 Hz) in dendrites could track the strong attenuation of backpropagating APs with distance from the soma (n = 7). Ultrafast (3.7 kHz) scanning revealed that the delayed initiation and peak of action potential propagating in distal dendrites could be resolved. Together, these results demonstrate ultrafast optical recording of electrical activity in multiple subcellular compartments.

IBRO – International Brain Research Organization

1-IBRO-175 Chronic cannabinoid exposure during adolescence disrupts sensorimotor gating and downregulates COMT function in the prefrontal cortex in rats

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Evidence from behavioral studies suggests that chronic exposure to cannabinoids during adolescence induce enhanced schizophrenia-like behavioral disruptions. Genetic studies have identified comethyl-o-transferase (COMT) as a putative susceptibility gene of schizophrenia disease. It can be postulated therefore that chronic cannabinoid exposure during adolescence maybe associated with a dysregulation in COMT expression and function. To test this hypothesis, adult animals undergoing chronic treatment of the synthetic cannabinoid receptor agonist WIN 55,212-2 (1mg/kg) during adolescence were subjected after 20 days washout period to prepulse inhibition of acoustic startle test (PPI), considered as a valid measure of sensorimotor gating in translational models of schizophrenia, and we examined the COMT levels and activity in the frontal cortex. Chronic WIN 55,212-2 exposure during adolescence caused disruption of PPI, does not affect COMT mRNA and protein levels but exhibited down-regulatory function in the prefrontal cortex. These results give further support to chronic exposure to cannabinoids during adolescence as a valid model of schizophrenia disease and identify a functional role for COMT in sensorimotor gating.

1-IBRO-176 Identification of a molecular mechanism leading to failure in neuroglial differentiation in focal cortical dysplasias (FCDs) offers clues to brain development

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Focal cortical dysplasia (FCD) is characterized by a spectrum of abnormalities in the development of the laminar structure of the human cerebral cortex, usually associated with cell abnormalities, giant/dysmorphic neurons, balloon cells and severe drug-resistant epilepsy. The mechanisms involved in the pathogenesis of type II FCD are not completely understood. Our main objective were to determine whether abnormal expression of microRNAs (miRNAs) could play a role in type II FCD and their potential

target genes to help clarify the pathophysiology mechanisms involved in type II FCD. We used total RNA isolated from brain tissue obtained after epilepsy surgery performed in 17 patients with type II FCD and 21 controls. MiRNA expression profile was assessed by microarray. We use bioinformatic approach to identify target genes. Quantitative PCR (qPCR), in situ hybridization (ISH) and luciferase report assay were used was to validate results. We identified highly expressed in our patients a development gene that is a pivotal regulator of mammalian neurogenesis, NEUROG2. We also found that the 5'-untranslated regions (UTR) of NEUROG2 is regulates by hsa-miR-34a, one of three miRNAs confirmed to be down expressed in type II FCD when compared with controls, the other two are: hsa-miR-31 and hsa-let-7f. Moreover, we also observed strong nuclear NEUROG2 expression in balloon cells. Then, our findings suggest that earlier failure in neuronal-glial differentiation and proliferation due to miRNAs deregulation could have happened during neocortical development in type II FCD.

1-IBRO-177 Iron-induced oxidative stress activates AKT and ERK1/2 and decreases Dyrk1B and PRMT1 in neuroblastoma SH-SY5Y cells.

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Iron is essential for proper neuronal functioning; however, excessive accumulation of brain iron is reported in Parkinson's, Alzheimer's, Huntington's diseases and amyotrophic lateral sclerosis. This indicates that dysregulated iron homeostasis is involved in the pathogenesis of these diseases. To determinate the effect of iron on oxidative stress and on cell survival pathways, such as AKT, ERK1/2 and DyrK1B, neuroblastoma SH-SY5Y cells were exposed to different concentration of FeCl2 (iron). We found that iron induced cell death in SH-SY5Y cells in a concentration-dependent manner. Detection of iNOS and 3-nitrotyrosine confirms the presence of increased nitrogen species. Furthermore, we found a decrease of catalase and protein arginine methyl-transferase 1 (PRMT1). Interestingly, iron increased the activity of ERK and AKT and reduced DyrK1B. Moreover, after FeCl2 treatment, the transcription factors c-Jun and pSmad1/5 were activated. These results indicate that the presence of high levels of iron increase the vulnerability of neurons to oxidative stress.

1-IBRO-178 Increased epileptic-like activity in synapsin-silenced Helix neurons associated with increased Ca2+ and Ca2+-activated BK currents.

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Synapsins are an evolutionarily conserved family of presynaptic proteins crucial for the fine-tuning of synaptic function. A large amount of experimental evidence has shown that synapsins are involved in the development of epileptic phenotypes in both humans and animals, however the exact mechanism is not clear. We examined how synapsin down-regulation through asRNA affects the firing single neurons and isolated monosynaptic circuits using neurons from Helix land snail. We found that synapsin silencing is associated with a hyperexcitable phenotype, increasing neuron excitability to electrical and pharmacological stimulation. Synapsin-silenced neurons show slightly depolarized resting membrane potential, decreased rheobase, reduced threshold of action potential firing and increased firing rates, with respect to control neurons. In addition, these neurons show increased drug-induced epileptic-like activity susceptibility. The observed increase of Ca2+ and BK currents in synapsin-silenced neurons seems related to changes in the shape of the action potential waveform. Both currents are responsible of the faster firing rate of synapsin-deficient neurons sustained by the increased after hyperpolarization

phase which helps recovering Na+ and Ca2+ channels during repetitive firing. This in turn speeds up the depolarization phase by reaching the action potential threshold faster. Our results provide evidence that synapsin silencing increases intrinsic cell excitability associated with increased Ca2+ and Ca2+-dependent BK currents in the absence of excitatory or inhibitory inputs.

1-IBRO-179 Functional changes in hippocampal neurons inducted by the effects of ApoE4 on AMPA-type channels

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Aging process induce impairment in cognitive process. The allelic variation of apolipoprotein E (ApoE4) has been associated ago over a decade with an increase in the risk of developing Alzheimer's disorder (AD). Previous studies show that this increase is due to the impairment in the synaptic plasticity process or to alterations in the ability of synapses to weaken or strengthen connections to other synapses in response to the environment. Deficits in synaptic plasticity that occur during aging process and AD probably are a result of alterations in expression and internalization of AMPA-type channels. We will evaluate the effects of apolipoprotein ApoE4 isoform on excitatory postsynaptic currents (EPSCs) of AMPA-type channels in hippocampal neurons of a mouse model of ApoETR using a whole-cell voltage-clamp method. Thus, we will compare the dynamic of LTP/LTD processes and the excitatory postsynaptic currents (EPSCs) of AMPA-type channels in hippocampal neurons of control mice with mice ApoETR. More recently, the ApoE4 has been involved in translation of neural signals, modulation of ionic channels, neurites outgrowth, synapse formation and neuronal migration. Accordingly, we expect that ApoETR mice show changes in the induction threshold and maintenance of LTP/LTD as well as variations in excitatory postsynaptic currents (EPSCs) mirroring the modifications in expression or internalization of AMPA-type channels processes. This model will allow elucidate the role of ApoE4 in the formation of memory and learning process and of synaptic plasticity.

Tuesday, May 31, 2016

A - Development

2-A-1 The Immune Role in Sexual Dimorphism

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Immune-brain communication influences behaviour and contributes to the development of the central nervous system (CNS) in a sexually dimorphic manner. The bed nucleus of the stria terminalis (BST) is a highly sexually dimorphic brain region; in most mammalian species the male BST is larger than the female BST. Previously, our lab has shown that mice lacking T cells due to knock out of the β and δ chains of the T cell receptor (TCRβ-/-δ-/-) have reduced anxiety-like behaviour. T cell deficient mice also show a loss in sexually dimorphic exploratory behaviour and several differences in brain volume including a lack of sexual dimorphism in volume of the BST. The present study focuses on microglia, the resident immune cells of the brain. Using immunohistochemistry and the microglial marker, anti-Iba1, microglia were examined in WT and TCRβ-/-δ-/- mice. Sex differences in brain volume of the BST are present early in postnatal life and this study encompassed microglia analysis of brain tissue from postnatal day 7 mice. Others have shown sex differences in microglia number and morphology in key

brain regions linked to anxiety. Using AxioVision microscope software, microglia soma are traced and number, perimeter, radius, feret ratio, and area in dorsal and ventral BST are quantified. Our results show sex differences in microglia number in BST in adult WT mice, however, this difference is absent in TCRβ-/-δ-/- adult mice. Ongoing analyses will determine if these results are also present early in the postnatal period.

2-A-2 The ENU-3 protein family members function in the Wnt pathway parallel to UNC-6/Netrin to promote motor neuron axon outgrowth in C. elegans.

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Steering of neurons to their final destinations depends on a number of different guidance cues and their receptors including those for Netrins, Slits, Semaphorins, and Wnts. Guidance of the DA and DB classes of motor neurons in C. elegans depends on UNC-6/Netrin and its receptor UNC-5 (Hedgecock et al., 1990). However, the axonal processes usually exit their cell bodies in the ventral cord in the absence of both molecules. A mutation in the enu-3.1 gene enhanced the low level of axon outgrowth defects of some of the DA and DB neurons found in the absence of either UNC-5 or UNC-6 (Yee et al., 2011). Five of the six members of the ENU-3 family are predicted to be trans-membrane proteins. We found that all of the ENU-3 proteins functioned to promote the outgrowth of the axons of the DA and DB classes of motor neurons in strains lacking either the guidance cue UNC-6 or its receptor UNC-5. Our evidence suggests that the ENU-3 proteins could be novel members of the Wnt pathway in nematodes.The ENU-3s function in a pathway parallel to the UNC-6/Netrin pathway for motor neuron axon outgrowth, most likely in the Wnt pathway.

2-A-3 The role of BDNF in Hebbian structural plasticity in the developing visual system

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Sensory experience-driven neuronal remodeling is a key step for the refinement and thus the proper wiring of the developing central nervous system. Sensory experience seems to be encoded as specific patterns of activity that can instruct stabilization of the "correct" and pruning of the "wrong" connections between neuronal partners. In the developing visual system, axons of neurons that are co-active with their neighbors stabilize their branches and synaptic contacts. Conversely, axons that fire out of synchrony with their neighbors destabilize and engage in exploratory branch growth. These findings are in line with the Hebbian learning postulate, summarized as "cells that fire together, wire together." Brain-derived neurotrophic factor (BDNF) is synthesized as a precursor protein (proBDNF) and its mature form (mBDNF) is derived by cleavage of the pro-domain. BDNF plays a key role in modifying the efficacy of synaptic plasticity, where proBNDF and mBDNF appear to have opposing functions. Using in vivo multiphoton imaging of retinal ganglion cells in developing Xenopus laevis tadpoles, combined with a visual stimulation leading to synchronous or asynchronous firing of an axonal input with its neighbors and pharmacological or genetic tools, we are able to identify molecular signals required for Hebbian learning. Our preliminary data suggest that correlated firing between a presynaptic cell and its postsynaptic partners requires mBDNF/TrkB signaling for synaptic stabilization. In contrast, proBDNF/p75NTR signaling promotes axonal branch loss in the developing visual system.

2-A-4 Role of HDAC2 in GABAergic Parvalbumin-positive cell maturation in basolateral amygdala

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Parvalbumin (PV) expressing basket cells, one of the largest subtypes of GABAergic interneurons in the brain, regulates cortical critical period (CP) plasticity, a developmental period, during which experience plays a major role in shaping brain connectivity. In particular, the maturation of PV cells, a process requiring dramatic changes in gene expression, determines CP closure. In adult mice, administration of histone deacetylase (HDAC) inhibitors reintroduced juvenile-like level of plasticity in visual cortex. Although most CP studies concentrated on sensory cortices, recent data suggested the existence of a critical period for erasure of fear memory in the basolateral amigdala (BLA), which may also be regulated by PV cell maturation. We hypothesized that Hdac2 is a master regulator of PV cell maturation in the BLA and that targeting HDAC2 expression in PV cell enhances fear memory erasure. We found that PV cell-specific Hdac2 knock-out mice showed reduced PV expression and putative PV perisomatic synapses around targeted neurons in the BLA. We are currently exploring whether fear expression following extinction is affected. These data suggest that HDAC2 function in PV cells is important for their synaptic plasticity in the BLA. Modulating Hdac2 activity in combination with behavioral therapy might be an effective treatment for post-traumatic stress disorder (PTSD) treatment.

2-A-5 Purkinje cell axon torpedoes in the developing mouse cerebellum

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Torpedoes are focal axonal swellings on cerebellar Purkinje cell axons, which are observed in aging, and in several forms of cerebellar disease. Torpedoes are also reported to exist transiently during development, although this has been poorly studied to date. Using a transgenic mouse that expresses eGFP at high levels in Purkinje cell axons, we studied torpedoes during postnatal development. We observed a transient increase of torpedoes in the developing mouse cerebellum that peaks at P11, with almost no torpedoes present before P7. One hypothesis for torpedo function in cerebellar disease is that they contribute to cell death. Since Purkinje cell death is largely complete by P7, our results suggest that developmental torpedoes do not contribute to cell death. The majority of developmental torpedoes we observed were oval, with only a small fraction (~7% at P11) located at axon collateral branch points. We found no significant differences in the proportion of branch point torpedoes over development, as might be expected if they played a role in collateral pruning, which occurs over the same age range when torpedoes are observed. Our findings suggest that in contrast to the putative role of torpedoes in cerebellar disease, developmentally-transient torpedoes are not associated with Purkinje cell death, although their function in cerebellar development needs to be further explored.

2-A-6 The functional requirement for clustered Protocadherin diversity in dendrite self-avoidance

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Dendrites of individual neurons develop non-overlapping arbors through a mechanism called neurite self-avoidance. By evenly spacing out their dendrites, neurons maximize their receptive fields for effective sampling of inputs and minimize the likelihood of making self-connections. In some cases,

neurons that exhibit self-avoidance, interact extensively with dendrites of neighbouring neurons of the same type suggesting that neurons can discriminate 'self' dendrites from 'non-self'. The clustered Protocadherins (Pcdhs), a large group of cell surface molecules, have been implicated in these processes as they provide enormous molecular diversity and single neuron identity. The Pcdh locus is divided into α, β, and γ clusters and encodes 58 isoforms, which are randomly and combinatorially expressed among individual neurons. We have shown that γ-Pcdhs mediate dendrite self-avoidance in cerebellar Purkinje cells (PCs). The objective of this study was to determine whether α-Pcdhs also signal in dendrite self-avoidance. To selectively label and analyze individual PCs, I injected an adenovirus expressing GFP into the cortices of neonatal mice. I report that, in mice lacking α-Pcdhs, the dendrites of individual PCs self-overlap extensively. PC survival in these mice is unaffected. We propose that α-Pcdhs contribute to dendrite self-avoidance through homophilic repulsion of sibling dendrites expressing the same set of Pcdh isoforms. To further our understanding of the functional significance of Pcdh diversity, we will analyze Pcdh mutants lacking multiple Pcdh members or subclusters.

2-A-7 Postnatal development of cerebellar Purkinje cell firing properties

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Purkinje cells are the sole projection neurons of the cerebellar cortex, and their firing represents the output of the cerebellar microcircuit. Purkinje cells display pacemaker-like properties: they fire action potentials at high frequency and high regularity even in the absence of synaptic input. We wondered how Purkinje cell firing is regulated during postnatal development. Using extracellular recordings from wildtype C57Bl/6 mice, we found that Purkinje cells in the first week of development had low firing frequency (P5−6: frequency=7.6Hz ±2.2, N=14 cells) with high precision of spike timing, as measured by the low coefficient of variation (CV) of inter-spike intervals (CV= 0.08±0.06). Surprisingly, during the second postnatal week of development, while Purkinje cell firing frequency increased (P10−14: frequency= 45.8Hz ±19.5, N=13), the firing precision decreased significantly (CV=0.15±0.04, P=0.005). We wondered whether GABA innervation, which changes dramatically during postnatal development, contributes to firing regularity during development but found no changes in Purkinje cell firing precision in the presence of GABAzine during the second week of postnatal development (P=0.79). This suggests that GABA does not contribute significantly to the regularity of firing during development as it does in older Purkinje cells. Since deficits in Purkinje cell firing precision has been implicated in several forms of ataxia, understanding the mechanisms that control Purkinje cell firing properties throughout development is important for our understanding of cerebellar function.

2-A-8 Roles of Semaphorin/Plexin signaling in synapse map formation in C. elegans

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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 fine neuronal map formation in the mammalian system. We are trying to tackle this question using Caenorhabditis elegans as a model system. C. elegans has a simple nervous system which consists of 302 neurons, enabling us to study neuronal map formation at single neuron/synapse level. We recently reported that 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. Plexin was recently shown to act as a RapGAP (Rap GTPase activating protein), which inactivates Rap small GTPase. Interestingly, we observed that both gain-of and loss-of functions of Rap-2, which is an ortholog of mammalian Rap2, mimicked the synaptic phenotype of plexin 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 at the meeting.

2-A-9 The Mesocorticolimbic Dopamine Pathway Exhibits A Phenotypic Plasticity To The Experience Of Early Life Adversity

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The capacity to select actions that lead to rewards while avoiding actions that lead to losses has both developmental and evolutionary advantages. The present study investigates individual differences in the capacity to learn from positive and negative feedback early in development. Typically developing children between the ages of 9-12 were recruited for a functional magnetic resonance imaging (fMRI) study. The fMRI protocol involved an instrumental learning task which required participants to learn to select stimuli that resulted in positive feedback and avoid stimuli that resulted in negative feedback. Results demonstrated that individual differences in the magnitude of the blood-oxygen-level dependent (BOLD) response in the ventral striatum (VS) correlated positively with the tendency to select stimuli that resulted in rewards. In contrast, greater BOLD responses in anterior insula (AI) and anterior cingulate cortex (ACC) were found when participants received losses compared to when they avoided losing. BOLD responses in the striatum correlated positively with the tendency to select the more rewarding stimulus. Furthermore, the presence of early life adversity positively correlated with BOLD responses in the VS to positive feedback; suggesting that the mesocorticolimbic dopamine pathway demonstrates a phenotypic plasticity to adversity experienced over the course of development.

2-A-10 Cellular mechanisms involved in retinoic acid-induced growth cone turning during neuronal regeneration

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The role of retinoic acid, the vitamin A metabolite, in development and regeneration is well known. In addition to generating trophic effects to initiate and maintain neurite outgrowth, there is accumulating evidence that retinoic acid acts as a chemoattractant for vertebrate spinal cord neurons. We have also shown that retinoic acid induces growth cone turning of cultured invertebrate motorneurons. Growth cones, found at the tips of developing or regenerating neurites, sense and integrate electrochemical information to direct neurite outgrowth. The cellular mechanisms underlying the chemoattractive effects of retinoic acid on neuronal growth cones are not well known. Our previous studies have determined that retinoic acid-induced growth cone turning involves localized retinoid X receptors (RXRs). We now present evidence that the retinoic acid receptors (RARs), also localized to the growth cones, may play a role in the chemoattractive response. In some cells, RXRs interact with signaling by Rac, a known regulator of growth cone behaviour. We now aim to determine the role of the small RhoGTPases, Cdc42 and Rac in retinoic acid-induced growth cone turning. These studies will further our

understanding of the tropic nature of retinoic acid, an important molecule in both nervous system development and regeneration.

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

2-B-11 Characterization of a synaptic vesicle binding site near the tip of the CaV2.2 C-terminal

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Calcium ion influx through voltage-gated calcium channels (CaV) triggers synaptic vesicle (SV) fusion and neurotransmitter release at active zones in presynaptic nerve terminals. Findings that a single CaV can trigger transmitter release suggested that SVs are held close to the CaVs by a molecular tether (Stanley, Neuron 1993) and we hypothesize that the channel intracellular regions participate in the tether mechanism. An SV binding site in the distal third (C3) of the channel C terminal was identified using a novel cell-free SV pull-down assay (SV-PD; Wong et al. Front Cell Neurosci 2013). More recently we restricted this site to a 49 amino acid sequence upstream from the tip of the CaV C-terminal (Wong et al. Front Cell Neurosci 2014). To further identify the specific binding site we synthesized five, non-overlapping 10 amino acid mimetic blocking peptides that span the putative binding region. SV-PD was carried out using a C3-region fusion protein as bait after pre-incubating the SVs with test mimetic peptides and SV capture was blocked by HQARRVPNGY. In a parallel FM-dye uptake assay we found that the same peptide markedly inhibited SV recycling. The RR*PNGY sequence within this peptide is highly conserved in CaV2.2 and CaV2.1 channels and may contribute to a novel SV binding domain.

2-B-12 Target-specific modulation of the cortico-raphe pathway by cannabinoids, but not serotonin

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Serotonin (5-HT) neurons located in the raphe nuclei modulate a wide range of behaviors by regulating the excitability of networks distributed throughout the entire brain. In turn, the raphe receives a vast array of synaptic inputs and a remaining challenge lies in understanding how these individual inputs are organized, processed and modulated in this nucleus to ultimately contribute to the core coding features of 5-HT neurons. The details of the long-range, top-down control exerted by the medial prefrontal cortex (mPFC) in the dorsal raphe nucleus (DRN) are of particular interest, in part because of its purported role in stress processing and mood regulation. Here, using a combination of immunohistochemistry, optogenetics and electrophysiological whole-cell recordings, we found that the mPFC provides a direct monosynaptic glutamatergic drive to both DRN 5-HT and GABA neurons that was conducive of a robust feedforward inhibition. Remarkably, activation of cannabinoid receptors dynamically reconfigured PFC information flow through the DRN circuit components, in effect shifting the excitatory-inhibitory balance governing the activity of 5-HT neurons. By modulating the processing features of the DRN, a mood-related subnetwork that gives rise to an expansive innervation pattern, this switch-like gating mechanism provides a flexible means to implement a concerted and distributed regulation of the excitability of large ensembles of brain networks, possibly to encode distinct behavioral states.

2-B-13 Netrin-1 is a potent regulator of synaptic function in the adult hippocampus

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Netrin-1 is a secreted protein that is critical for normal neural development, directing cell and axon migration during embryogenesis, however little is known about its role in adulthood. Here, we show that the adult mouse hippocampus expresses a relatively high level of netrin-1, suggesting a potential role in synaptic plasticity underlying learning and memory. Brief bath application (5 mins) of netrin-1 rapidly increases dendritic spine volume, as well as the frequency of AMPA-mediated excitatory postsynaptic currents recorded in CA1 pyramidal neurons, indicating a role in the modulation of glutamatergic synaptic transmission. Further, exogenous netrin-1 induces a dose-dependent potentiation of evoked synaptic responses in acute brain slices from adult mouse by increasing AMPA receptor mediated current. Additionally, conditional deletion of netrin-1 in CA1 pyramidal neurons attenuates activity-dependent long-term potentation. Together, these findings demonstrate that netrin-1 is a potent regulator of synaptic plasticity in the adult brain.

2-B-14 State- and frequency-dependent modifications of medial temporal lobe activity following deep brain stimulation in macaques

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Deep brain stimulation (DBS) has been applied to various brain structures in an attempt to selectively alter neural activity associated with disease states. For fornix stimulation (FS) of the hippocampus (HC), the optimal frequency of stimulation, and the effectiveness of a given protocol across differing ongoing brain-behaviour states is less well understood, but has widespread implications for treatment strategies. We therefore recorded neural activity in the medial temporal lobe in response to FS that varied in frequency, across two states. Two rhesus macaques received FS in single pulses of 40/100 Hz, and in trains of 10 bursts delivered at several intervals from 1.25-13 Hz. A chronically-implanted multi-electrode array sampled LFPs from different sites in HC and subicular complex, as the animals were stimulated during a goal-directed memory task and during quiescent periods that included sleep. Neural responses varied as a function not only of inter-burst frequency but also of state. In general, shorter interval evoked stronger theta/alpha-band power during resting states than during attentive, goal-seeking states. These results suggest that changes in stimulation patterning may alter its influence on targeted pathways, and the same stimulation protocol varies in its effective response as a function of behavioural state, supporting further investigation of responsive/closed-loop state-contingent stimulation including stimulation during sleep. Brain Canada, Alzheimer's Association, Alzheimer's Society of Canada, Krembil Foundation, NSERC DG, NSERC CREATE VSA (TKL, OT).

2-B-16 Mechanism of asymmetric electrical coupling between a pair of cardiorespiratory neurons

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Electrical synapses, formed between neurons through cell-to-cell channels called gap junctions, allow for reliable transmission and synchronization of action potentials. The present study concerns an electrically coupled two-neuron network in the CNS of the gastropod mollusc, Lymnaea stagnalis. The peptidergic

neurons, identified as Visceral Dorsal 1 (VD1) and Right Parietal Dorsal 2 (RPD2), innervate aspects of the cardiorespiratory system and form an asymmetric electrical synapse. Using dual sharp-electrode current clamp recordings in isolated brain preparations, the hypothesis that differential input resistance generates asymmetric coupling was tested. The input resistance of VD1 was greater than that of RPD2. Upon hyperpolarization, the input resistance and coupling coefficient of RPD2 increased, while those of VD1 remained stable. This suggests that the RPD2 resting conductance is voltage-dependent and reduced at more negative voltages. Under physiological conditions, VD1 controls the firing of both cells, so the asymmetric coupling achieved through differential input resistance may ensure that RPD2 follows VD1. Given their involvement in cardiorespiratory function, we also tested the hypothesis that the VD1/RPD2 network is sensitive to changes in oxygen levels. Initial results indicate that conditions mimicking a stressful aquatic environment (hypoxia or hypercapnia) alter synaptic input to the VD1/RPD2 system. In summary, these findings provide a mechanism for asymmetric electrical synapses as well as a basis for how coupled neurons respond to environmental changes.

2-B-17 Developing Multi-Compartment Models of Interneuron Specific 3 (IS3) Cells in Hippocampus Using a Semi-Automated Approach

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Determining how intrinsic properties govern and modulate neural input-output processing is a critical endeavour for understanding microcircuit functions in the brain. Here we focus on uncovering the intrinsic properties of interneuron-specific type 3 (IS3) cells in hippocampus, which, to date remain uncharacterized. In this work, data on electrophysiological characteristics of IS3 cells was acquired, and two-photon calcium imaging was used to assess the spread of back-propagating action potentials in IS3 cell dendrites. Using this data as a target reference, we developed a semi-automated approach to generate IS3 cell models. In this approach we generated databases of multi-compartment models, each one possessing unique combinations of ion channel types and conductance values. The rationale for the choices of ion channel types used were based on electrophysiological features, other hippocampal interneurons and in situ hybridization data from the Allen Mouse Brain Atlas. From our model databases we identified those with parameter ranges whose measurements most closely resembled those seen in experimental traces, and then analyzed the effects of different intrinsic properties on IS3 cell spike generation. Given the present correspondence with data, our models predict relative conductance balances of different channel types in IS3 cells as well as the impact of different channel type combinations on spike generation. Moving forward, our models can serve to investigate the functional roles of IS3 cells in the hippocampus, a central structure in memory formation.

2-B-18 Calcium Responses to Single Action Potentials in Spinal Cord Lamina I Neurons

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Lamina I neurons of the spinal cord are a hub of nociception, taking in nociceptive information from the periphery, processing it, and relaying it to the brain. In chronic pain models, lamina I neurons exhibit hyperexcitability and decreased inhibition. Voltage-gated calcium channels (VGCCs) have been implicated in the development of chronic pain, however their function in lamina I neurons is poorly understood. Here, we develop an approach to measure calcium responses evoked by single action

potentials (APs) in these neurons. We made current-clamp recordings of lamina I neurons, loaded via the patch pipette with the calcium indicator Oregon Green Bapta-1 (OGB1). APs were induced by current injection. Simultaneous two-photon imaging of OGB1 fluorescence in the somata, dendrites, and dendritic spines of lamina I neurons enabled calcium response analysis. Single APs induced robust ΔG/R increases in the somatic cytosol (peak ΔG/R = 0.1, n= 58 cells), nucleus (peak ΔG/R = 0.04, n= 58 cells), dendrites (peak ΔG/R = 0.2, n=75 dendrites) and dendritic spines (peak ΔG/R = 0.1, n=14 spines). Calcium responses were ablated by tetrodotoxin, and greatly reduced in the presence of nickel and NNC-55-0396, demonstrating a major role of T-Type VGCCs. The role of other VGCCs was also investigated. These findings suggest that single APs induce a calcium rise in the dendritic arbour and nucleus which occurs predominantly through T-type VGCCs. Action potential induced calcium influx through VGCCs could aid integration of inputs and alter gene transcription to upregulate excitability.

2-B-19 New evidence for the involvement of BDNF and pro-BDNF in the regulation of aggressive behavior

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Brain-derived neurotrophic factor (BDNF) plays crucial role in neuronal survival, development, differentiation and plasticity. It is known that mice with decreased BDNF expression including knockout and conditional knockout showed increased intermale aggression. In our study we focused on BDNF expression in Norway rats selectively bred for 82 generations for high level of aggression towards to man or its absence. Considerable differences between highly aggressive and nonaggressive rats were shown both in BDNF mRNA and protein levels. Significantly increased BDNF mRNA level was found in the frontal cortex (FC), raphe nuclei area of midbrain (RN), nucleus accumbens (NA) of aggressive rats compared to nonaggressive rats. BDNF mRNA levels in the hippocampus (HP) and substantia nigra (SN) were unaltered. At the same time, significantly increased BDNF level as well as pro-BDNF level was found in the HP and NA of aggressive rats compared to nonaggressive rats. We also had found that BDNF protein level was increased in the striatum. In the RN of aggressive rats increased pro-BDNF protein level was observed between aggressive and nonaggressive rats. In the FC of nonaggressive rats only pro-BDNF level was increased. BDNF/proBDNF ratio was decreased in RN, HP, NA of aggressive rats while the ratio was increased in FC. Thus, for the first time it was shown that BDNF and proBDNF contribute to the genetically defined aggressiveness in rats. The work supported by the Russian Scientific Foundation (#14-25-00038)

2-B-20 Astrocyte independent neurovascular coupling

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Ca2+ dependent pathways in neurons and astrocyte endfeet can initiate arteriole diameter changes to control local perfusion. Discrepancies between the clear involvement of Ca2+ transients in astrocyte endfeet in brain slices versus controversial endfeet signals in vivo during functional hyperemia, prompted us to determine whether astrocytes are essential contributors to synaptic activation-induced arteriolar dilation. Imaging synthetic and genetic (GCaMP) Ca2+ indicators in acute rat brain slices of the sensory cortex with 2-photon fluorescent microscopy, we discovered a threshold of synaptic activation below which astrocyte endfeet Ca2+ transients are absent in response to brief, moderate electrical stimulation (termed subthreshold stimulation) that evokes arteriole dilation. Subthreshold stimulation-

evoked neuronal Ca2+ transients and vasodilation was significantly reduced by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-receptor blockage but not by N-methyl-D-aspartate receptor inhibition. Blocking nitric oxide synthesis attenuated vasodilation but had no effect on Ca2+ signals. Phospholipase A2 and D inhibition, as well as inward rectifier- and Ca2+-sensitive potassium channel inhibitors had no effect. Two-photon imaging of astrocyte endfeet Ca2+ signals showed no activation prior to functional hyperemia in response to a 5s air puff to the whisker in the barrel cortex of awake, active mice. In summary we show evidence that sensory stimulation does not recruit astrocyte endfeet to mediate functional hyperemia.

2-B-21 Effects of phosphorylation on neurosteroid-induced modulation of GABAA receptor currents

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Neurosteroids are well known modulators of GABAA receptor activity. GABA receptor mediated mIPSCs recorded from pyramidal neurons cultured for ≥14 days decay in two phases, one lasting about 10 ms (τ1) and second lasting about 50 ms (τ2). Neurosteroids like THDOC affect mIPSCs usually by altering (both shortening and prolonging) these decay rates. However, previous studies have reported highly variable effects of neurosteroids on the decay and amplitude of mIPSCs. We have hypothesized this variability may be dependent on phosphorylation state of GABAA receptors. Here we have examined the activity of the neurosteroid THDOC on GABA mediated mIPSCs after treatment with compounds that activate various kinases. In general, we found that kinase activity altered the efficacy of neurosteroid activity although each kinase had differing and specific effects. Activation of PKC using phorbol ester PMA prolonged τ2 to a less extent than in untreated recordings (300 % versus 225%). However, the effect on τ1 was smaller in THDOC/PMA treated cells resulting in about the same change of charge transfer in both conditions. THDOC, after activation of PKA activity, increased the amplitude of mIPSCs and prolonged the duration of τ2, increasing transfer by about 300%. Finally, THDOC after activation of the TrkB by DHF reduced mIPSCs amplitude, increased the rate of τ1 while prolonging the τ2. The combination of these three outcomes resulted in no change in the charge transfer. These data show that kinase activity greatly determines the activity of THDOC on GABAA receptor mediated mIPSCs.

2-B-22 Persistent postanesthetic memory deficits are mediated by an inflammatory pathway

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Introduction: General anesthetics trigger persistent memory deficits by increasing a tonic GABAA receptor (GABAAR)-mediated inhibitory current in the hippocampus (J Clin Invest, 2014). The underlying mechanisms are uncertain. The same tonic current is also increased by a pro-inflammatory cytokine IL-1β, via the p38-MAPK-dependent signaling pathway (Cell Rep, 2012). Therefore, we tested the hypothesis that an IL-1β-dependent signaling pathway mediates anesthetic-induced increase in tonic GABA current, which in turn underlies persistent memory deficits. Methods: Co-cultures of murine hippocampal neurons and cortical astrocytes were co-treated with etomidate (1 μM) and other drugs for 1 h. The drugs were then washed out and whole-cell voltage clamp techniques were used to record tonic GABA current 24 h later. Western blot assays were performed to measure IL-1β levels in hippocampal tissue collected from mice 24 h after injection with etomidate (8mg/kg, intraperitoneal). Results: An anti-inflammatory drug minocycline (100 μM) prevented etomidate-induced increase in

tonic GABA current. Western blot showed that etomidate enhanced IL-1β levels in hippocampal tissue. The increase in tonic GABA current was reversed by the IL-1β receptor antagonist, IL-1Ra (100 ng/mL), and an inhibitor, SB 203,580 (20 μM) of a downstream factor of the IL-1 receptor, p38-MAPK. Conclusion: The anesthetic-induced persistent increase in GABAAR-mediated tonic current, which underlies postanesthetic memory deficits, is mediated by an inflammatory signaling pathway that involves IL-1β and p38-MAPK.

2-B-23 Exploring the energetics of a high-frequency neuronal oscillator using computational models

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Action potentials are energetically costly, as ion concentration gradients must be re-established at the cost of ATP. Weakly electric fish sense their surroundings using a high-frequency Electric Organ Discharge (EOD). A specialized brain area known as the pacemaker nucleus sets the EOD timing; with each EOD, every one of the approximately 150 neurons in the pacemaker synchronously fires an action potential. Since these fish continuously generate the EOD at a high rate for their entire life, they have likely evolved mechanisms to minimize the energetic cost of each action potential. The energy consumed by an action potential is impacted by the relative kinetics of the ion currents involved. To determine the ion channel combinations that can give rise to high-frequency oscillations while minimizing energetic cost, we have explored the parameter space of a previously-described model of pacemaker neurons. We found that these constraints are met in a relatively small region of parameter space, suggesting that ion channel expression may be tightly regulated in this system to minimize cost. The biological validity of parameter values in this region will be investigated through future in-vitro studies.

2-B-24 Oscillations promote neuronal discrimination of EPSP events with single neurons and population codes

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Oscillations are a hallmark of cortical activity in both in vivo and in vitro preparations. Synchronous oscillations, where cells spike in close temporal contiguity, can be advantageous to neuronal coding by promoting reliable responses to stimuli. Conversely, cells can generate asynchronous activity, characterized by out-of-phase spikes, which is shown to decorrelate responses to stimuli, in turn promoting information processing in local circuits. While models of can be tuned to generate both synchronous and asynchronous spikes, it remains unclear how these two modes of activity may contribute to information processing. Here, we employ computer simulations to examine how the injection of oscillations may enhance the ability of single neurons and whole recurrent networks to discriminate amongst incoming spike trains. Consistent with experimental work, oscillations improved the ability of single neurons to discriminate between stimuli. We found that when synaptic inputs from a recurrent network were added, stimulus discrimination based on single neuron responses was hindered by the presence of spontaneous background activity. This problem, however, can be largely overcome by considering mean population activity across neurons. Synchronous oscillations yielded the highest level of discrimination for a wide range of parameters. In addition, our results show that neuronal

networks may take advantage of different coding strategies. We suggest that living neuronal networks may use several different coding strategies depending on the requisites of information processing.

2-B-25 Expression and roles of K+ channels (Kir2.1, Kv1.3) in microglial anti-inflammatory states: Proliferation and migration

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After CNS damage, microglia can enter anti-inflammatory, alternative activation and acquired deactivation states that help resolve classical activation and promote repair. The population of microglia at damage sites will depend on both proliferation and migration, which are Ca2+-dependent. The driving force for Ca2+ entry (membrane potential) is regulated by K+ channels. Kir2.1 and Kv1.3 are prevalent in microglia; thus, we asked whether Kir2.1 and Kv1.3 contribute to Ca2+ influx, proliferation and migration of rat microglia in anti-inflammatory states. In unstimulated rat microglia, Kir2.1 (encoded by KCNJ2) and Kv1.3 (KCNA3) were highly expressed compared with other family members. Kir2.1 mRNA and currents were comparable in unstimulated microglia and in alternative activation (IL-4 treated) and acquired deactivation (IL-10) states. Kv1.3 mRNA and currents depended on the activation state. We then examined the functional roles of Kir2.1, using Ba2+ and ML133. Both blockers slightly increased proliferation in unstimulated cells and after IL-4 treatment (but not IL-10). Migration and chemotaxis were increased by IL-4 and by IL-10, and both functions were greatly reduced by blocking Kir2.1. Under all activation conditions tested, blocking Kir2.1 greatly reduced Ca2+ influx through Ca2+-release-activated Ca2+ (CRAC) channels. Thus, Kir2.1 is necessary for microglial Ca2+ signaling and migration in resting and anti-inflammatory states. Work on the functional roles of Kv1.3 is ongoing, and will be presented at the meeting.

2-B-26 NMDA receptor elevation of cytosolic reactive oxygen species strengthens GABAergic signaling

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Recent work from our lab has shown that GABAergic signaling is strengthened by cytosolic reactive oxygen species (ROS) elevated by insulin signalling (Accardi et al (2015)). Whether GABAergic synapses can also be potentiated by ROS generated at glutamatergic synapses has yet to be examined. To address this question, we investigated the putative crosstalk between glutamatergic and GABAergic synapses of molecular layer interneurons of the mouse cerebellum. Whole-cell recordings from individual stellate cells was used to study activity-driven GABAergic plasticity. Specifically, an extracellular stimulating electrode was placed in the molecular layer of the cerebellum to activate excitatory parallel fibers (PFs) from granule cells and neighbouring inhibitory interneurons. As anticipated, activation of extrasynaptic NMDARs by high-frequency stimulation of PFs elevated cytosolic ROS. This in turn caused a time-dependent increase in the strength of GABAergic synapses. The use of pharmacological blockers suggest that the origin of ROS generated by NMDAR activation is due to the combined activities of neuronal nitric oxide synthase and neuronal NADPH oxidase. Taken together, our data reveal that ROS generated by the activity of extrasynaptic NMDARs is a novel mechanism for the strengthening of GABAergic transmission.

2-B-27 Morphine-mediated phosphorylation of the P2X7 receptor critically gates analgesic tolerance

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Morphine is indispensable in the treatment of acute and chronic pain; however, its use is limited by the development of analgesic tolerance. The microglial ATP-gated P2X7 receptor (P2X7R) is critically involved in the development of morphine tolerance. In the present study, we examined the expression and function of microglial P2X7Rs after repeated morphine treatment, and the role of P2X7Rs in the development of morphine analgesic tolerance. In adult male Sprague Dawley rats, repeated morphine treatment caused a progressive decline in morphine anti-nociception and a loss in morphine analgesic potency. Morphine tolerant animals and morphine treated BV2 cells displayed an up-regulation of P2X7R expression and a potentiation of P2X7R ion channel function. We next tested whether receptor phosphorylation played a role in the potentiation of P2X7R function. Daily co-administration of a protein kinase inhibitor with morphine prevented the morphine-induced potentiation of BzATP-evoked calcium influx and inward current. Using P2X7R mimetic peptides and mutant P2X7R constructs, we identified the specific site of morphine-mediated phosphorylation on the P2X7R that contributes to changes in function. Blocking site-specific phosphorylation of P2X7R significantly attenuated the development of morphine tolerance. Taken together, our findings demonstrate that morphine-mediated phosphorylation of microglial P2X7Rs critically gates the development of morphine analgesic tolerance.

2-B-28 Correlated synaptic inputs drive dendritic calcium amplification and cooperative plasticity during clustered synapse development

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The mechanisms that instruct the assembly of fine-scale features of synaptic connectivity in neural circuits are only beginning to be understood. Using whole-cell electrophysiology, two-photon calcium imaging and glutamate uncaging in hippocampal slices, we discovered a functional coupling between NMDA receptor activation and ryanodine-sensitive intracellular calcium release that dominates the spatiotemporal dynamics of activity-dependent calcium signals during synaptogenesis. This developmentally regulated calcium amplification mechanism was tuned to detect and bind spatially-clustered and temporally-correlated synaptic inputs, and enacted a local cooperative plasticity rule between coactive neighboring synapses. Consistent with the hypothesis that synapse maturation is spatially regulated, we observed clustering of synaptic weights in developing dendritic arbors. These results reveal developmental features of NMDA receptor-dependent calcium dynamics and local plasticity rules that are suited to spatially guide synaptic connectivity patterns in emerging neural networks.

2-B-30 The role of PAK signaling in the entorhinal cortex in the regulation of synaptic plasticity and social memory

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Social cognition is an extraordinarily complex memory process that shapes the formation and maintenance of social bonds. Autism spectrum disorders (ASD) are characterized by distinct impairments in social engagement, and are associated with single gene mutations. PAKs (p21-activated kinases) are a family of serine/threonine protein kinases that are; target enzymes of Rho small family GTPases and central regulators of actin cytoskeleton, neuronal morphology, and involved in synaptic

and behavioural plasticity. However, the molecular mechanisms that underlie the role of PAK signaling in the pathophysiology of ASD remain elusive. We generated a transgenic mouse model where the spatiotemporal expression of a dominant negative PAK mutation in the entorhinal cortex is modulated. The tetracycline inducible system allows us to analyze the role of PAKs in the regulation of both synaptic transmission and plasticity, and behavioural responses without potential developmental perturbations. We found that mutant PAK mice have impaired social memory. Furthermore, the memory deficits were fully rescued with a tetracycline analog that blocks the expression of the PAK transgene. We identified that the entorhinal-hippocampal connections in mutant mice have reduced basal synaptic strength, plasticity, and enhanced paired pulse facilitation. Ultimately, PAK signaling in the entorhinal cortex regulates neuronal transmission, long-lasting synaptic plasticity, and social memory through the activation of the Rho signaling pathway and subsequent cofilin-dependent actin regulation.

2-B-31 Glycine primes depression of NMDA receptor-mediated synaptic transmission in pyramidal neurons but not interneurons in the CA1 region of the hippocampus

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N-methyl-D-aspartate receptors (NMDARs) are activated upon simultaneous binding of co-agonists glycine and glutamate. We reported previously that stimulating the glycine site primes the NMDARs endocytosis in neurons acutely isolated from the hippocampus. The preparation of acutely isolated neurons contains both pyramidal neurons and interneurons and NMDARs in this preparation are primarily somatic. Here we investigated whether glycine might differentially prime NMDARs between pyramidal neurons and interneurons at hippocampal synapses by using acute brain slices taken from rats. We treated slices with glycine (200 μM, 5 min) and found that after washing out glycine there was a progressive decline of NMDAR-mediated excitatory post-synaptic currents (EPSCs) recorded from pyramidal neurons (n = 9 cells). In contrast, the same treatment of glycine had no effect on NMDAR-EPSCs recorded from CA1 interneurons located in the layer of stratum radiatum (n=6 cells). These findings indicate that applying glycine selectively primes depression of synaptic NMDAR responses of CA1 pyramidal neurons but not interneurons. We also found that NMDAR-EPSCs in pyramidal neurons did not decline after glycine treatment when dynasore (50 μM), a cell-permeable small molecule inhibitor of dynamin, was applied through whole-cell patch pipette (n= 5 cells). Collectively, our findings suggest that NMDARs at synapses in hippocampal pyramidal neurons but not in interneurons may be primed for internalization by glycine in a dynamin-dependent manner, leading to depression of NMDAR synaptic transmission.

2-B-32 Presynaptic NMDA receptors act via RIM1αβ to control the readily releasable pool in neocortical layer-5 pyramidal neurons

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Presynaptic NMDA receptors (preNMDARs) have been found at several central synapse types where they typically enhance vesicle release, but the downstream molecular machinery by which they do so remains unknown. We explored if preNMDARs rely on the presynaptic scaffolding and vesicle pre-priming protein RIM1. Spontaneous and evoked release onto layer-5 pyramidal cells were recorded with

quadruple patch clamp in visual cortex acute slices from P11-17 mice. In control slices, preNMDAR blockade reduced the frequency of spontaneous release, suggesting a reduced release probability. PreNMDAR blockade also decreased evoked responses, but only for spike frequencies above 8 Hz. Since spontaneous release rate was ~2.5 Hz, these findings seemed contradictory. Also, preNMDARs increased release probability indirectly, by upregulating the replenishment rate of the readily releasable vesicle pool. In conditional heterozygous RIM1αβ KO mouse slices, both evoked response amplitude and paired-pulse depression were decreased, implying a lowered baseline release probability. As in controls, preNMDAR blockade lowered the rate of spontaneous release in RIM1αβ KO slices. Surprisingly, evoked responses in RIM1αβ mutants were unaffected by preNMDAR blockade. In conclusion, preNMDARs increase release probability during high-frequency spiking via RIM1αβ. PreNMDAR control of spontaneous release, however, does not rely on RIM1αβ. This unexpected difference in RIM1αβ dependence of preNMDAR function mirrors the difference in frequency dependence between evoked and spontaneous release.

2-B-33 Molecular mechanisms of IGF-1 on the growth cone guidance in developing motoneuron.

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The path-finding of developing neurons subject to the guidance of both attractive and repulsive cues emerge in the way to their target. The binding of guidance cues to receptors on a growth cone trigger a series of signaling pathways that result in dynamic cytoskeleton rearrangements and alter the direction of axon growth. The discoveries that expression of IGF-1 (insulin-like growth factor-1) in the developing skeletal muscle increase with the formation of differentiated skeletal muscle fibers and decrease to very low adult levels during the process of synapse elimination. Although evidence suggests that insulin-like growth factor plays an important role in the development and growth of the neuromuscular synapse, the effect of IGF-1 in the guidance on the growth cone of a motoneuron remains unknown. Here we focus on the possibility and underlying molecular mechanisms of IGF-1 in the guidance of a developing neuron by using 4 to 10 hours (embryonic development) and 1-day-old (mature stage) primary cultured motoneurons of Xenopus laevis. The chemical gradient of IGF-1 on a growth cone can be achieved by micropipette at 1 Hz in frequency, 50 msec in duration and 3 psi with a microinjector. The growth rate of developing axons was increased and the growth cones were significantly attracted toward to the direction of IGF-1 application. Pretreatment of tyrosine kinase inhibitor genistein effectively occluded growth turning response induced by IGF-1. The IGF-1-induced guidance effect was not abolished when calcium was eliminated from the culture medium or there was bath applicatio

2-B-34 Rapid postsynaptic cAMP modulates synapse structural potentiation (sLTP)

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Postsynaptic cAMP signaling is a crucial for synaptic plasticity such as the protein synthesis-dependent late phase of long-term potentiation (L-LTP). However, the spatiotemporal role of cAMP in structural plasticity (sLTP) remains elusive. Here we provide evidence for a rapid postsynaptic cAMP/PKA function in sLTP, independent of the protein synthesis signaling, by two-photon live imaging and optogenetic techniques, which can monitor and manipulate cAMP levels at individual synapses. By monitoring postsynaptic cAMP dynamics during LTP, we detected transient NMDA receptor-dependent cAMP

production in the postsynaptic structure called dendritic spines along with the dendrite during L-LTP induction, but not the early-phase (E-LTP), indicating cAMP signaling in L-LTP. Next, to address the cAMP function in the structural plasticity, we induced L-LTP at some spines and induced sLTP at the unaffected neighbouring spines on the same neuron. We found a cAMP/PKA-dependent prolonged spine enlargement during sLTP following neighboring synapse L-LTP induction, suggesting a role of cAMP in sLTP and also a possible crosstalk mechanism. We also mimicked the cAMP production by two-photon photoactivation of photoactivatable adenylyl cyclase (PAC) in sLTP, and confirmed the rapid cAMP/PKA but not protein synthesis-dependent function, and also found cAMP is necessary within 1 min time window after sLTP induction, suggesting the cAMP signaling is a crucial component for rapid sLTP. We will discuss how postsynaptic cAMP regulates structural plasticity.

2-B-35 Binding Affinity of Guanosine to the G1 Receptor

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Guanosine is a purine nucleoside that when released extracellularly can result in a myriad of physiological effects in vitro and in vivo. For example, extracellular guanosine (Guo) can affect the growth, differentiation and survival of various cell types. Guo has also been shown to protect the CNS from insults, inhibit apoptosis, and stimulate the release of growth factors from cells. However, to date, its mechanism of action remains unclear. Preliminary studies have suggested that a high-affinity binding site for Guo exists in the rat brain. Based on pharmacological and transductional evidence and bioinformatic research, our lab has identified an orphan G-protein coupled receptor as the first putative Guo receptor (G1R). In an unpublished pilot study we showed that Guo inhibits apoptosis in Drosophila Schneider 2 (S2) cells transfected with the G1R but fails to do so in non-transfected (wild type) S2 cells that do not endogenously express G1R. These results indicate that these effects may be mediated specifically by the G1R. This study aims to further examine the Guo-G1R relationship using transient G1R transfections in the S2 cell model. We are currently using a series of binding assays using tritiated Guo to determine the binding affinity of Guo for G1R. We seek to confirm chemical and functional binding of Guo to G1R and that G1R is a distinct purinergic receptor for Guo. Findings from this study are important to further understand the nature of this receptor, and may aid in the development of neurorestorative and neuroprotective treatments involving Guo.

2-B-36 Sex Differences in Microglia and P2X4 Receptor Mediation of Neuropathic Pain in Rats

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Microglia are fundamental in mediating peripheral nerve injury (PNI)-induced pain hypersensitivity in rodents. PNI produces upregulation of P2X4 receptors (P2XRs) on spinal microglia. P2X4R activation induces release of brain-derived neurotrophic factor (BDNF), which activates neuronal TrkB and induces downregulation of the potassium chloride co-transporter KCC2 in spinal dorsal horn neurons. Recently, we discovered that microglia and P2X4Rs mediate pain hypersensitivity in male but not female mice. Here, we determine whether sexual dimorphism in pain signalling exists in rats. Neuropathic pain was induced using the sciatic cuff model (PNI) and mechanical hypersensitivity measured using von Frey fibers. PNI produces robust microgliosis and upregulation of genes associated with microglial reactivity in the dorsal horn of the spinal cord in both sexes. However, intrathecal application of minocycline (300 ug), a non-specific microglia inhibitor, reverses pain hypersensitivity in male but not female rats.

Additionally, intrathecal injection of TNP-ATP (30 nmol), a P2X1-4 receptor inhibitor, alleviates hypersensitivity in males only. Furthermore, upregulation of P2rx4 occurs after PNI in males but not females. Thus, we demonstrate that the sex difference in microglia-neuron signalling in mice is generalizable across rodent species. PNI does produce microglia reactivity in female rats; however, microglia and P2X4Rs do not mediate pain hypersensitivity in females. This sex difference demonstrates the necessity of including female rodents in preclinical pain research.

2-B-37 Neuronal correlates for bi-directional adaptation of the hypothalamic-pituitary-adrenal (HPA) axis during chronic stress.

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Repeated restraint stress (RRS) is a well-established chronic stress model that concurrently causes two opposing changes in the hypothalamic-pituitary-adrenal (HPA) axis: habituation to the repeated stressor (i.e. restraint) and sensitization to a novel stressor. The underlying neural and synaptic plasticity mechanisms for this versatile HPA axis adaptation are unknown. Corticotropin releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVN) are the output neurons of the HPA axis. Here, we report that RRS induced two subpopulations of PVN-CRH neurons with opposing (increased and decreased excitability) electrophysiological properties. CRH TdTomato reporter mice (male, 6-8 weeks old) were used to conduct whole-cell patch clamp recording from PVN CRH neurons in acute brain slices. Mice received daily 1-h restraint for 21 consecutive days. On the 22nd day, we examined afferent glutamatergic synaptic transmission and intrinsic excitability. We found that RRS primed the glutamate synapses to express long-term potentiation (LTP) following trains of afferent stimulation. Importantly, LTP occurred only in a subpopulation of CRH neurons (55%). The remaining CRH neurons that did not express LTP were characterized by a decrease in intrinsic excitability with a longer delay to first spike and a decrease in the frequency of action potentials following depolarizing current injections. The priming for LTP may support a sensitized response to a novel stressor, whereas the decrease in intrinsic excitability may support habituation to the repeated stressor.

2-B-38 Theta Burst Neural Activity Alters Resting Astrocyte Ca2+ and Arteriole Tone

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Astrocytes respond to synaptic activity and change arteriole diameter via specialized endfeet processes that enwrap vessels. It is well known that astrocytes signal by large transient changes in intracellular Ca2+ concentration, but the role of resting astrocyte Ca2+ is less well described. Recent evidence shows that a drop in resting astrocyte Ca2+ using intracellular Ca2+ chelators causes a vasoconstriction in adjacent arterioles. To test for a functional link between changes in resting astrocyte Ca2+ and blood vessel regulation we used two-photon microscopy and recorded changes in intracellular astrocyte Ca2+ levels using Rhod-2 AM following theta burst electrical stimulation in acute cortical slices. Following 50s of stimulation, we observed a significant, prolonged decrease in resting astrocyte Ca2+ levels. Successive stimulations compounded this decrease, with each stimulation producing a new, lower baseline. Glutamate receptor antagonists targeting N-methyl-D-aspartate receptors (NMDARs) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) prevented this effect suggesting the involvement of glutamatergic synaptic transmission. Concomitant with the drop in resting Ca2+ levels in astrocytes, theta burst stimulation evoked a long-lasting constriction in neighbouring arterioles. This

vasoconstriction was also prevented with NMDAR antagonists. Together, these findings enhance our understanding of how astrocyte resting Ca2+ levels may help regulate vasculature in response to specific patterns of synaptic activity.

2-B-39 Origins of voltage-gated sodium and calcium channels in primordial single-celled eukaryote Salpingoeca rosetta

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We have isolated a complement of gene homologs from the simplest extant eukaryotic species to possess voltage-gated sodium (Na+) and calcium (Ca2+) channels. Recent evidence suggest that single cell bacteria use voltage-gated potassium channels to transmit long range signals through biofilms. We envisage that these homologs of voltage-gated Ca2+ and Na+ channels found in single cell choanoflagellate Salpingoeca rosetta may generate Ca2+-dependent action potentials that signal between cells of choanoflagellate colonies, regulate intra-cellular events, or control movement of it's single flagellum or cilia. The full complement of Ca2+and Na+ channels in Salpingoeca include an L-type calcium channel (SroCav1), T-type calcium channel (SroCav3), and a sodium channel (SroNav2). SroNav2 codes for an 1831 amino-acid transmembrane protein of four repeat domains with a selectivity filter ring, DEEA, resembling Ca2+-selective sodium channel genes found exclusively in non-vertebrate animals. Transfection and expression of SroNav2 in Human Embryonic Kidney-293T (HEK-293T) cells generates a voltage-dependent Ca2+ current. SroNav2 is structurally similar to Nav1 sodium channels but is impermeable to sodium ions. Characteristically, calcium as a charge carrier can be replaced in most calcium channels by divalent barium, however SroNav2 is impermeable to barium ions, operating as a dose-dependent blocker of the Ca2+ current. We are interested in evaluating this unusual calcium-selective channel that is impermeable to barium ions, and to understand the roles SroNav2 may play in Salpingoeca.

2-B-40 NMDA receptor/CaMKII signaling modulates firing properties in cerebellar stellate cells

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In the cerebellum, a region classically associated with motor coordination and learning, the stellate cell is one of several subtypes of GABAergic inhibitory interneurons found in the cerebellar cortex. We have observed a novel form of NMDA receptor-mediated firing rate modulation that increases inhibitory signaling within the cerebellar micro-circuit. Performing cell-attached electrophysiological recordings of stellate cells yielded no increase in spontaneous action current frequency during baseline, but a local application of NMDA induced a persistent increase in spike rate. Repeating cell-attached recordings with high K+ internal pipette solution induced a similar chronic increase in spontaneous action currents but is blocked by bath application of NMDA receptor antagonist. During whole-cell current clamp recordings these cells exhibit a passive increase in step-evoked AP frequency as well as a hyperpolarization of spike threshold. Inhibiting the activity of CaMKII, but not protein kinase C, blocked the hyperpolarization of AP threshold. Voltage clamp experiments elucidate the development of a persistent inward current as well as a large outward current that both depend on CaMKII activity. Further investigation into the signaling cascade responsible for this firing rate increase has physiological relevance as a novel regulatory

mechanism of inhibitory circuits. Our work will provide new insight into the role of NMDA receptor-dependent excitability modulation in the cerebellar micro-circuit.

2-B-41 Regulation of entorhinal cortical input to hippocampal granule cells by local inhibitory network in the dentate gyrus

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Interneurons in the molecular layer of the dentate gyrus (DG) play a crucial role in the integration of entorhinal cortex (EC) input to the hippocampus. EC input activates various types of locally interconnected neurons and the resulting network response will shape the firing pattern of granule cells (GCs) via fast and slow inhibitory signals. Electric stimulation of the perforant path (PP) evoked unusually long lasting hyperpolarization (LLH) in GCs. Decrease in the rate of action potential firing of GCs was significantly decreased for several seconds following PP stimulation. LLH was most efficiently induced with fast, short trains and was dependent on the activation of postsynaptic GABA and mGluR1 receptors. In order to differentiate between the effect of EC inputs and the direct activation of local interneurons on LLH, ChR2 was expressed in cells of the medial entorhinal cortex (MEC). Light activation of axons arriving from the MEC successfully induced LLH. The resulting IPSPs were smaller in amplitude but highly similar in duration and in their capacity to decrease GCs excitability. LLH was selectively triggered by the activation of the feed-forward inhibitory circuit. Furthermore, LLH developed in an age-dependent manner as GCs recordings from 3 age groups showed significant differences in PP-evoked responses. LLH is a unique feature of the EC-DG synaptic network and could play a role in the sparsification of cortical information within the hippocampus.

2-B-42 PV+ Interneurons Constrain the Lateral Amygdala Engram to a Sparse Representation

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During the formation of Pavlovian threat memories, plasticity in the lateral amygdala (LA) associates neutral, unconditioned stimuli with an aversive, unconditioned stimulus. Although ~70% of principal neurons in this region receive the requisite sensory projections to form this association, many studies suggest that only 10-20% of cells participate in the memory trace, or engram. Both experimental and computational research suggests that this sparsity is the result of a process of competition in which only the most excitable cells are allocated to the engram. However, the exact mechanisms by which this process occurs are unkown. Here, using Arc expression during memory retrieval as an indicator of the engram, we show that 12% of LA neurons are active regardless of the strength of memory expression. Furthermore, using genetically targeted inhibitory DREADDs, we show that this proportion expands when the activity of PV%2B interneurons are impaired during encoding. In line with predictions from recent modeling studies, these results suggest that inhibition plays a central role in memory allocation, constraining the LA engram to a sparse population of neurons and ensuring the stimulus specificity of learned defensive behaviour. Sparse distributed coding schemes have been well-described in the cortex and my be a central feature of engrams throughout the brain.

2-B-43 Dexmedetomidine prevents an anesthetic-induced persistent increase in GABAA receptor current

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Introduction: Persistent cognitive deficits after anesthesia and surgeries contribute to poor long-term outcome, yet there are no treatments available. We recently showed that persistent hyperactivity of γ-aminobutyric acid type A receptors (GABAARs) contributes to postanesthetic memory deficits (JCI, 2014). The α2-adrenergic receptor agonist dexmedetomidine (Dex) has been shown to reduce anesthetic-induced delirium (Psychosomatics, 2009). Here, we tested the hypothesis that Dex prevents the anesthetic-induced persistent increase in tonic GABA current. Methods: Co-cultures of murine hippocampal neurons and cortical astrocytes were treated with etomidate (Etom 1 μM) ± Dex (10 μM) for 1 h and then washed. Tonic GABA current was recorded 24 h later using whole-cell voltage clamp techniques. In some studies, the α2-adrenergic receptor antagonist (yohimbine 5 μM) or agonist (clonidine 100 μM) was co-applied with Dex. Results: Etom alone increased tonic GABA current to 160% of control. Co-treatment with Dex reversed the Etom-induced increase. Yohimbine prevented Dex reversal of the etomidate increase in current whereas clonidine mimicked the effects of Dex. Conclusions: Dex acts on α2-adrenergic receptors to prevent the etomidate-induced persistent increase in tonic GABA current. Future studies will determine whether DEX can be 'repurposed' as a simple and safe strategy to prevent postanesthetic memory deficits.

2-B-44 Non-convulsive seizures observed from adult mice following middle cerebral artery occlusion: Involvement of hippocampal circuitry

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The hippocampal circuitry is known to be vulnerable ischemic injury and genesis of seizures or epileptiform activities. However, the role of hippocampus in genesis of acute post-ischemic seizures in a rodent model of middle cerebral artery occlusion (MCAO) remains to be examined. We explored this in adult C57 black mice (7-11 months-old) using permanent or reversible MCAO via intraluminal suture insertion protocols. Acute post-MCAO seizures were detected via simultaneous behavioral monitoring and electroencephalographic (EEG) recordings from hippocampal and parietal cortical areas, and histological assessments of brain injury were performed at 24-48 hours of 2-4 weeks post MCAO. We also examined regional hyperexcitable responses in mouse brain slices in vitro using hypoxia-hypoglycemia episodes. Non-convulsive seizures were observed in animals within 2 hours following MCAO and featured with hippocampal or hippocampal-cortical discharges. Of the discharges recorded from ipsilateral hippocampal and cortical areas, the hippocampal discharges were more robust and time advanced relative to cortical discharges or occurred alone without accompanying cortical discharges. When examined in vitro, population hyperexcitable responses following HH episodes were observed from the hippocampal CA3 area but not in hippocampal CA1, dentate gyrus and parietal cortical areas. Taken together these observations suggest that the hippocampal circuitry may play a significant role in genesis of electrographic seizure activity early following brain ischemia.

2-B-45 Netrin-1 Regulates Mitochondrial Dynamics in Oligodendrocytes

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Mitochondria in the CNS generate the carbon chains crucial for myelin biosynthesis, and their dysfunction has been linked to neurodegenerative diseases, including multiple sclerosis. Despite the

importance of mitochondria in myelin development and maintenance, how these organelles migrate and function within oligodendrocytes is poorly understood. Netrin-1 promotes myelin expansion by oligodendrocytes. Receptors for netrin-1 are enriched at paranodal junctions and their deletion results in severe disruption of the myelin sheath. We have characterized the morphology and dynamics of mitochondria in oligodendrocytes in response to netrin-1 and have identified a novel mitochondrial docking protein expressed by oligodendrocytes. Mitochondria remain tubular and elongated in response to high concentrations of netrin-1 but become severely fragmented when pathways downstream of netrin-1 are inhibited. Additionally, we have shown that mitochondria are highly motile and migrate within the cell towards local concentrations of extracellular netrin-1. The mitochondria remain aggregated at sources of netrin-1 over time, which appears to be facilitated by the interaction between netrin-1 and a mitochondrial docking protein. These findings reveal a link between extracellular netrin-1 and the distribution and function of mitochondria within oligodendrocytes.

2-B-46 Synaptic gain control in the neuroendocrine stress axis

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During chronic stress, the hypothalamic-pituitary-adrenal (HPA) axis can become habituated or sensitized depending on the nature of the stressor. Despite its importance in stress pathophysiology, the neural mechanisms underlying this versatility of HPA axis stress responsiveness is poorly understood. Here, we examined plasticity of afferent glutamate synapses onto coritcotropin-releasing hormone (CRH) secreting neurons in the paraventricular nucleus of the hypothalamus (PVN) - the output neurons of the HPA axis - in two models of chronic stress in mice: repeated restraint stress (RRS) and chronic variable stress (CVS), to model habituation and sensitization, respectively. One day after the last stress challenge, we prepared acute brain slices and made whole-cell patch clamp recordings from PVN CRH neurons. We found that, in comparison to no-stress controls, RRS decreased synaptic multiplicity (the number of release sites per axon) without changing the frequency of miniature excitatory postsynaptic currents (mEPSCs). By contrast, CVS increased both synaptic multiplicity and mEPSC frequency. These data support the idea of bidirectional plasticity of glutamatergic synapses onto HPA axis output neurons in directions consistent with the changes in the neuroendocrine sensitivity to stress. Further work will determine if plasticity of glutamate receptor composition as well as the dynamic properties of these synapses following chronic stress also occurs and potentially contributes to plasticity of the neuroendocrine stress response.

C – Disorders of the Nervous System

2-C-47 Amyloid- β Clearance by Glia of wild-type and FAD amyloid

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One of the hallmarks of Alzheimer disease (AD) is the accumulation of amyloid peptides into plaques. According to the "amyloid hypothesis," the pathogenesis of AD is triggered by the accumulation of the toxic amyloid-β (Aβ) peptides that are produced from the amyloid precursor protein (APP). This pathological cascade could be precipitated by an imbalance between the production and clearance of Aβ peptides. Since glia are known to play essential roles in CNS clearance processes, including Aβ uptake and degradation, we investigated the molecular mechanisms of Aβ clearance and glial functions in

primary rat glial cultures. As a model for FAD, we used a mutation at the α-secretase cleavage site of APP (APP770 K687N/Aβ K16N) that we previously identified (Kaden et al, 2012). The resulting Aβ42 K16N peptide was resistant to degradation by neprilysin and also protected wild-type Aβ42 peptide. Treatment of primary rat glial cultures with Aβ42 K16N synthetic peptide both decreased cell viability in MTT reduction assays and increased expression of markers of glial activation, as assessed by immunostaining, only in the presence of wild-type peptides. However, mutant Aβ42 peptide alone appeared to be taken up faster than either wild-type Aβ42 or a hetero-mixture of the two peptides. Moreover, ELISA and mass spectrometry analyses point to a distinct pattern of Aβ degradation products also appears to be generated. Thus, the α-secretase K16N mutation appears to impact glial cell clearance activity and points to a novel pathway of toxicity.

2-C-48 Exploring the effect of scyllo-inositol treatment on the transcriptome in a mouse model of Alzheimer's disease

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scyllo-Inositol treatment was shown by McLaurin and colleagues to reduce amyloid load and reverse behavioural changes in TgAD mouse model of Alzheimer's disease (Nat Med 2006). Fenili and colleagues discovered that scyllo-inositol is a competitive inhibitor of myo-inositol transport across the blood brain barrier (Mol Med 2007). Regulation of brain myo-inositol levels is a common activity shared by several different mood stabilizing drugs. Human clinical trials found scyllo-inositol treatment to reduce aggression and agitation in a subset of patients with Alzheimer's disease. This project aims to identify pathways that are affected by scyllo-inositol treatment. We hypothesize that scyllo-Inositol treatment has both Aβ dependent and Aβ independent effects that contribute to the results seen in clinical trials. Going back to the animal model, Affymetrix mouse genome 430 2.0 arrays were used to evaluate the gene expression in 6 month old TgAD and nontransgenic littermates given scyllo-inositol ad libitum for 1 month. Gene expression changes were analyzed with Qiagen Ingenuity Pathway Analysis and Database for Annotation, Visualization and Integrated Discovery. Calcium signalling and synaptic transmission pathways were most significantly modulated both transgenic and nontransgenic animals. The altered pathways were not restricted to the TgAD mice and are implicated in neuropsychiatric disorders. It is suggested from our data that the neuropsychiatric effects of scyllo-inositol treatment may be mediated through Aβ independent mechanism.

2-C-49 GSK-3β specific inhibitor, TDZD-8, is neuroprotective against neonatal hypoxic ischemic brain injury

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Glycogen synthase kinase 3β (GSK-3β) is a constitutive multifaceted kinase that plays a critical role in several neurophysiological processes. Dysregulation of GSK-3β leads to neuronal cell death following ischemia-reperfusion injury in adults but its effect in neonates is less clear. However, it is known that expression levels of GSK-3β are higher in the neonates than the adults implicating a role of GSK-3β in neonatal hypoxic ischemic brain injury. TDZD-8 is a non-ATP competitive inhibitor specific for GSK-3β that has neuroprotective, antioxidative and anti-inflammatory properties. In this report, we investigated the effects of GSK-3β inhibitor TDZD-8 on neuroprotection against hypoxic-ischemic brain injury in

neonatal mice. We showed that pre-treatment with TDZD-8 significantly reduced brain infarct volume and improved sensorimotor function following the hypoxic-ischemic brain injury. TDZD-8 reversed the reduction of phosphorylated protein kinase B (Akt) and GSK-3β, and suppressed the activation of caspase-3 induced by the hypoxia-ischemia. Furthermore, we found that TDZD-8 reduced the hypoxic-ischemic induced apoptotic cell death and reactive astrogliosis which could link the Akt/GSK-3β/caspase-3 pathways. We conclude that GSK-3β plays an important role in neonatal hypoxic-ischemic brain injury, and can serve as a potential drug target for neonatal hypoxic-ischemic brain injury.

2-C-50 Microstimulation-induced tremor oscillations in human globus pallidus

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Helmich's Dimmer Switch Model (2012) states that the basal ganglia is responsible for initiating 3 - 7 Hz tremor, and the cerebellum modulates tremor amplitude, but direct evidence for pacemaker oscillators in the human basal ganglia is lacking. The globus pallidus internus (GPi) is an important output nucleus of the basal ganglia which sends inhibitory projections to the motor thalamus, an important site for tremor control by implantation of deep brain stimulation (DBS) electrodes. Data from 94 GPi neurons across 15 patients was collected and analyzed from Parkinson's disease (PD) vs. dystonia/dystonia related diseases) during mapping for DBS implantation. 15 border cells were identified in the PD patients and 9 were found in the dystonia patients. It was found that the PD neuronal population had a significantly higher baseline firing rate than in dystonia (92.2 ± 37.7 Hz vs. 52.9 ± 27.2 Hz, $p<0.0001$). The border cell firing rate average was 48 ±17.2 Hz in PD patients which was not different from the dystonia border cell firing rate of 20.2 ± 11.9 Hz ($p=0.10$). Border cell firing rates were found to be significantly lower than GPi firing rates in both disease groups (PD, $p< 0.0001$, dystonia, $p<0.01$). Of these border cells, 7 showed evidence of being induced into a tremor oscillation in the absence of tremor. 5 oscillatory cells were found in PD patients while 2 were found in the dystonic-related disease ("control") group. These results show that border cells in GPi may be autonomous pacemakers that play a role in tremorgenesis in dystonia and PD.

2-C-51 Effects of a nutraceutical formulation on hippocampal neurogenesis, brain-derived neurotropic factor and memory in the 3xTg-AD mouse model of Alzheimer's disease

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Alzheimer's disease (AD) is devastating neurodegenerative condition. Early mitochondrial dysfunction, oxidative stress, and inflammation precede AD onset. AD cognitive symptoms are linked to brain-derived neurotrophic factor (BDNF) loss in humans, rodents and other species and to reductions in adult neurogenesis in rodents. Antioxidants and anti-inflammatory factors elevate levels of neurogenesis and BDNF in animals, suggesting that in combination they may delay AD. We administered a multiple ingredient dietary supplement (MDS) to triple-transgenic (3XTg-AD) and normal mice from 1-7 months of age. The MDS was formulated to target age-related changes in oxidative stress, inflammation, mitochondrial function, membrane integrity and insulin resistance. Relative to vehicle treated controls, supplemented 3XTg-AD mice showed increased neurogenesis, correlated with BDNF expression.

Preliminary findings indicate that the MDS may also improve spatial memory. These results suggest that the MDS raises BDNF levels, increasing neurogenesis and improving memory in a mouse model of AD.

2-C-52 A simple network simulates symptoms of schizophrenia by integrating functions of inhibitory, excitatory, and neuromodulatory systems

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The ability to appropriately attribute relevance to ideas or environmental stimuli may be a core process that is compromised in schizophrenia. We develop a network-level computational model to show how deficits in value-assignment can emerge from disrupting feed-forward inhibition. Specifically, we show how manipulations of network inhibition can alter the behavioral phenomena of latent inhibition and blocking in a manner consistent with patterns observed in schizophrenia. By pairing this model with an amygdala-like output network, we simulate behaviors following pharmacological, chemogenetic, and optogenetic manipulations to the rodent frontal cortex. The model postulates that total projection neuron activity in medial frontal cortex can be treated as a scalar code for relevance, and that inhibitory neuron plasticity is regulated as the difference between this and signals for unconditioned reinforcers. Together, this work offers a computational theory of schizophrenia gating deficits and highlights the importance of inhibitory neuron plasticity and modulation.

2-C-54 Interaction between Alzheimer's Disease and Metabolic syndrome

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Alzheimer's disease (AD) is a debilitating neurodegenerative disease. Diabetes and metabolic syndrome (MS) represent a risk factor for dementia later in life and might contribute to its course in a co-morbidity case. The intake of high-caloric Western diet (HCD) is associated with incidence of these conditions. We hypothesize that a transgenic rat model of AD maintained on a HCD will exhibit more severe cognitive impairment and display increased cellular pathologies compared to the wild type rat on a HCD and rats on a control diet. Wild type with intact genotype and transgenic, carrying two human mutations of β-amyloid precursor protein, rats 8.5-9 month old were fed either a HCD or a control diet for 12 weeks. Assessed physiological parameters included body weight, glucose and insulin levels, serum lipid profile and blood pressure. Cognitive function was assessed using Morris water maze. Immunohistochemical staining was used to examine neuroinflammation. Rats maintained on the HCD developed significant obesity, visceral adiposity, dyslipidemia and hyperinsulinemia, but did not become hypertensive. Glucose metabolism was altered only in wild type rats on the HCD. Memory consolidation was impaired in the co-morbid model of AD and MS. Immunohistochemistry has shown greater white matter neuroinflammation in the co-morbid model in comparison to MS alone. Our data suggests that neuroinflammation might be one of the key elements linking early brain pathology to the neurodegeneration observed in AD and indicates anti-inflammatory agents may be a potential treatment strategy.

2-C-55 4-Aminopyridine alleviates ataxia and reverses cerebellar cortical output deficiency in a mouse model of spinocerebellar ataxia type 6

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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 that encodes the α1A subunit of P/Q-type Ca2+ channel that is enriched in cerebellar Purkinje cells. Using a knock-in mouse model that harbors 84-CAG repeat, we observed motor deficits at 7 months in homozygous SCA684Q/84Q mice. SCA684Q/84Q Purkinje cells exhibit reduced firing rate (56±4 Hz, n=27 cells) and a reduced precision of spike timing (measured by the coefficient of variation, CV, of interspike intervals, 0.14±0.01 ms) compared to wildtype (WT) control cells (firing rate: 72±6 Hz, n=30 cells, $P<0.05$; CV: 0.09±0.01 ms, n=30 cells, $P<0.001$). We observed motor deficits in heterozygous SCA684Q/+ mice at 19 months and found that Purkinje cells exhibit a reduced precision of spike timing compared to age-matched WT cells ($P<0.005$) without any significant change in firing rate ($P=0.71$). We then tested the effect of potassium channel blocker 4-aminopyridine (4-AP) on 7-month-old SCA684Q/84Q Purkinje cells and found that it improved precision of spike timing to WT levels (CV: 0.10±0.01, n=11 cells, $P<0.01$) without affecting firing rate ($P=0.15$). Chronic oral administration of 4-AP alleviated 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, $P<0.0001$). These results provide a novel therapeutic approach for the treatment of motor deficits in SCA6.

2-C-56 Combinational Therapeutics in Alzheimer Disease: A Novel Treatment Paradigm

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Amyloid-beta (Aβ) peptide is one of the primary targets for therapeutic intervention in Alzheimer Disease (AD), however no successful treatment has been developed. Mono-target therapeutics have focused on either inhibiting Aβ formation or promoting clearance, but never both. To this end, we evaluated the potential for combination therapy targeting multiple aspects of the Aβ pathway as a treatment paradigm. We hypothesized that a single-dose of Aβ antibody would decrease cerebral Aβ and activate microglial cells, while subsequent small molecule therapy would affect sustained removal, offering greater benefit over mono-therapy. TgCRND8 mice were thus treated at 5 months of age with either BAM10 antibody administered via MRI guided focused ultrasound to open the blood brain barrier followed by scyllo-inositol, scyllo-inositol alone (SI) or untreated. SI was administered ad libitum in drinking water for one month and all mice were sacrificed at 6 months. Staining for Aβ revealed a significant decrease in plaque load between the control group and both treatment groups, but no significant change between the two treatments. Similarly, there was a significant decrease in astrogliosis and a decreasing trend in microgliosis between control and treatments. Three-dimensional analysis also revealed increased phagocytosis of Aβ by microglial cells, demonstrating a novel mechanism of SI in activating microglia in AD.

2-C-57 After intracerebral hemorrhage, oligodendrocyte precursors proliferate and differentiate inside white-matter tracts in the rat striatum

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Damage to myelinated axons contributes to neurological deficits after acute CNS injury, including intracerebral hemorrhage (ICH). Potential treatments to promote re-myelination will require fully differentiated oligodendrocytes; however, almost nothing is known about their fate following ICH. Using a rat model of striatal ICH, we quantified survival, proliferation and differentiation of oligodendrocyte-lineage cells (Olig2+) in the peri-hematoma region, surrounding striatum and contralateral striatum from 1 to 28 days. In the peri-hematoma, t¬¬he density of Olig2+ cells increased dramatically and peaked at 7 days, coinciding with fragmentation of myelinated axon bundles. Very little proliferation (Ki67+) of Olig2+ cells was seen in the subventricular zone from 1 to 28 days. However, by 3 days, many were proliferating locally in the peri-hematoma region. By 14 days, their density declined in the peri-hematoma region and, by 28 days, it was the same as the contralateral striatum. At 14 and 28 days, many surviving axons were aligned into white-matter bundles, which appeared less fragmented. Oligodendrocyte maturation was prevalent over the 28 day period. Densities of immature oligodendrocyte precursor cells (OPCs; NG2+Olig2+) and mature (CC-1+Olig2+) oligodendrocytes in the peri-hematoma increased dramatically over the first week. Regardless of the maturation state, they increased preferentially inside the white-matter bundles. Thus, endogenous OPCs proliferate and differentiate in the peri-hematoma region and have the potential to re-myelinate axon bundles after ICH.

2-C-58 Defining the circuitry of Infantile Spasms using the Ts65Dn mouse model.

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Infantile spasms (IS) is a childhood seizure disorder characterized by extension and/or flexion,cognitive deterioration and bursts of epileptiform activity separated by an electrodecremental response (EDR). Children with Down Syndrome (DS) are especially vulnerable to IS and so we have chosen to use a mouse model of DS, the Ts65Dn (Ts) mutant mouse to model IS. An IS phenotype can be induced in Ts by administration of a GABAB receptor agonist. Previous studies in humans have implicated the role of the cortex, thalamus and brainstem in the maintenance of IS. However, the origin and directionality of spread of IS is currently unknown. We aim to define the circuitry of IS using depth electrodes implanted in the cortex (primary motor, primary sensory), thalamus (ventral, dorsal, nRT) and hippocampus (DG, CA1). We used the approach of phase synchrony, which demonstrate EEG signals as instantaneous phase angles, from which a distribution of the phase differences between two signals may be created. We also used Cross-correlation analysis between signals to provide measures of latency between signals. Noise signals were revealed in EEG recordings with principal component analysis and they were removed from the original signals. We determined that IS involves an abnormal cortico-thalamo-hippocampal circuit activity, where the epileptiform activity in the cortex leads that in the thalamus which in turn leads that in the hippocampus. This study is important for the mechanistic knowledge gained, and for the therapeutic potential of ablation studies to prevent the spread of IS.

2-C-59 PAOPA - A promising drug candidate for neuropsychiatric disorders and its neuroprotective effects through increased expression of neurotrophic factors

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Neuro-inflammation is the primary pathological feature of many disorders and conditions such as stroke, multiple sclerosis, Alzheimer's and Parkinson's disease, and schizophrenia. Current treatment for

schizophrenia focuses on antagonism of receptors such as dopamine and serotonin, but more effective treatments may arise from also decreasing neuro-inflammation. Our lab has been studying one of the most potent allosteric modulators of the dopamine D2 receptor, PAOPA (3(R)-[(2(S)-pyrrolidinylcarbonyl)amino]-2-oxo-1-pyrrolidineacetamide), as a potential and promising drug for schizophrenia. PAOPA is able to reverse and prevent biochemical and behavioural abnormalities observed in the amphetamine-sensitized and the MK-801 induced preclinical models of schizophrenia. However, the molecular mechanisms through which it attenuates these abnormalities are not well known. In this study, we investigated the effects of PAOPA on the mRNA expression of neurotrophic factors which may reduce neuro-inflammation. SH-SY5Y neuroblastoma cells were treated with increasing concentrations of PAOPA. Expression of cerebral dopamine neurotrophic factor (CDNF), brain derived neurotrophic factor (BDNF), and mesencephalic astrocyte-derived neurotrophic factor (MANF) were quantified using real-time qPCR. We report that PAOPA altered the expression of all three neurotrophic factors, suggesting it may play a role in the reduction of neuro-inflammation. This novel finding advances the development of PAOPA as a drug candidate for schizophrenia, and potentially other diseases involving neuro-inflammation.

2-C-60 Functional Integration Of New Cortical Neurons Following Focal Stroke

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Ischemic stroke enhances the proliferation of stem and progenitor cells (PCs) in the adult brain and a significant portion of PCs migrate from the subventricular zone to regions surrounding the stroke-induced infarct. Whether these cells are capable of integrating into the damaged cortical space and contributing to stroke recovery is unknown. To examine the progenitor cell populations following stroke, we produced photothrombotic-induced infarcts in transgenic reporter mice: the Nestin-GFP line, where the Nestin-expressing PCs are labelled with GFP, and the Doublecortin-DsRed line, where the immature neuronal population are labelled with DsRed. Cortical infarcts elicited an increased number of Nestin-GFP cells surrounding the stroke region. While the majority of these cells were identified as oligodendrocytes and astrocytes, approximately 5% of these newly generated cells were identified as immature neurons. By using a double transgenic mouse that labels both the nestin and doublecortin population, immature neuroblasts could be identified surrounding the stroke-induced infarct. These neurons shared many of the characteristics of early stage adult-generated olfactory bulb granule cells, including the capacity to fire action potentials. Importantly, many of these cells also showed spontaneous postsynaptic currents, demonstrating their capacity to functionally integrate. This is the first demonstration to show that at least some of these cells can integrate into the injured cortex and are positioned to potentially contribute to long-term stroke recovery.

2-C-61 Characterizing Spontaneous Recovery of Motor Function Following Cortical and Subcortical Stroke

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Stroke is a leading cause of neurological disability and a majority of patients have long-term motor impairments, often as a result of damage to the motor cortex and/or striatum. While both humans and animals show spontaneous recovery following stroke, little is known about how injury location affects the recovery process. This information is essential in order to develop new therapies to enhance

recovery. In this study we used endothelin-1 (ET-1), a potent vasoconstrictor, to produce focal infarcts in the forelimb motor cortex, the dorsolateral striatum or both the cortex and striatum in male Sprague-Dawley rats. The spontaneous recovery profile of the animals was followed over an 8-week period using four behavioural tasks assessing motor function and limb preference to identify how recovery varies depending on injury location. All three models resulted in functional deficits on the Montoya staircase, beam, and cylinder tasks but no significant impairments were seen in the adhesive removal task. The three groups demonstrated distinct patterns of recovery on the behavioural tasks with the combined cortical plus striatal group having the largest and most persistent impairments overall. These results suggest that the pattern of recovery is not simply dependent on lesion volume but on lesion location and the behavioural test employed. Moreover, damage to the striatum is an important predictor of the level of post-stroke motor recovery. All three models produce sustained motor impairments that will be valuable in assessing novel, adjunctive post-stroke therapies.

2-C-62 Inhibitory Synaptic Transmission and KCC2 Function in the Motor Cortex of the Presymptomatic 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 upper and lower motor neurons. Recent studies performed in the SOD1-G93A familial mouse model of ALS have observed reductions in KCC2 gene expression as well as membrane expression in spinal cord motor neurons. Similar studies in the SOD1-G93A mouse model have also found an increase in network hyperexcitability in presymptomatic cultured spinal cord motor neurons. Thus, the main objective of this study is to determine if hyperexcitability in the primary motor cortex results from a reduction in KCC2 expression and thus, a reduction in the strength of inhibitory synaptic transmission. Using immunofluorescent labelling and western blot analysis of the upper motor cortex, we found that KCC2 at both excitatory and inhibitory synapses is significantly reduced in the presymptomatic SOD1-G93A mouse. This reduction in KCC2 is correlated with a decrease in cell size. We are currently determining whether these effects result in changes in synaptic strength by recording spontaneous inhibitory postsynaptic currents. Evidence from this study suggests that KCC2 function is compromised in the upper motor neurons of the presymptomatic SOD1-G93A mouse which could provide novel insights into the pathogenesis of ALS.

2-C-63 Toward a valid animal model of alcohol use disorder in schizophrenia: an assessment of face, predictive and construct validities

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Alcohol use disorder commonly occurs in patients with schizophrenia and contributes greatly to its morbidity. Unfortunately, very few options are available for the treatment of co-occurring alcohol use disorder and schizophrenia. While the atypical antipsychotic clozapine can reduce alcohol use in patients with schizophrenia; clozapine's toxicity has severely limited its use in patients. To understand the mechanisms underlying, and to develop medications for, co-occurring alcohol use in schizophrenia, we have recently developed a novel rat model of alcohol drinking in schizophrenia based upon the neonatal

ventral hippocampal lesion (NVHL) rat. Briefly, ventral hippocampi in post-natal day (PND) 7 male Sprague-Dawley rat pups were injected with either excitotoxic ibotenic acid (NVHL) or aCSF (sham). Rats were weaned on PND21 and then given access to 10% alcohol in a 2-bottle preference design between PND28-42. Upon reaching adulthood (PND90), animals are re-exposed to 20% alcohol and allowed to establish stable drinking. Upon stable drinking, animals (n=10/group) were treated with vehicle, clozapine (8 mg/kg) or haloperidol (0.8 mg/kg). The NVHL rat, like patients with schizophrenia, drinks more alcohol than sham rats under both continuous and intermittent access paradigms (2.5- and 3-fold, respectively), and reduces its alcohol drinking when treated with clozapine, and not haloperidol. These findings help validate the NVHL rat as a model of alcohol use disorder in schizophrenia, in which we can now test the efficacy of potential medications and study underlying mechanisms.

2-C-64 SUMO1 over-expression in adult neurogenesis and Alzheimer's disease pathology

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Modification of proteins by Small Ubiquitin-related Modifiers (SUMOs) can influence protein trafficking, processing and aggregation. Studies suggest that high levels of SUMO1 may exacerbate Alzheimer's disease (AD) and it has been reported that the AD-related Amyloid Precursor Protein (APP) can be SUMOylated in vitro. Our recent study showed that transgenic mice over-expressing SUMO1 display neuronal dysfunction and memory defects. In this work, we set out to understand how increased SUMO1 may influence AD progression in vivo. We found that SUMO1 transgenics (Tg) have fewer neural progenitors in the hippocampus and an increase in immature and mature neurons. BrdU injections revealed that new born neurons do not mature properly, resulting in the dysfunctional neurons associated with SUMO1 over-expression. To investigate the SUMO1 links to AD pathology, SUMO1 Tg mice were crossed with an AD mouse model of amyloid pathology expressing high levels of APP. The SUMO1-APP double Tg mice did not exhibit any changes in APP processing but have increased insoluble Aβ and plaque density compared to the APP only Tg mice. Correspondingly, the SUMO1-APP mice have reduced dendritic spine densities and more profound memory defects. We hypothesize that SUMO1 affects the clearance of Aβ, possibly by microglia and/or extracellular proteases. This study suggests that the main impact of SUMO1 on AD is on removal of the amyloid aggregates as opposed to protein processing and highlights the differences between SUMO1 and SUMO2/3 in their potential contributions to AD pathology.

2-C-65 DIXDC1 phosphorylation and control of dendritic morphology is impaired by rare genetic variants

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The development of dendrite morphology and synapses are essential for brain function and disruption of these processes is associated with Autism spectrum disorders (ASDs). Dix domain containing 1 (DIXDC1) has previously been implicated in neurodevelopmental disorders, but its role in postnatal brain function remains unknown. Using a knockout mouse model, we determined that DIXDC1 is a novel regulator of excitatory dendrite and spine development in the cortex. We also discovered that the ASD-risk gene MAP/microtubule affinity-regulating kinase 1 (MARK1) phosphorylates DIXDC1 to regulate

dendritic and spine development by modulating the actin network. Finally, rare missense variants in DIXDC1 were identified in individuals with ASD using genetic sequencing. Interestingly, these rare variants inhibit DIXDC1 phosphorylation, causing impairment to dendrite and spine growth. These data reveal that DIXDC1 is a novel regulator of cortical dendrite and synaptic development, and provide mechanistic insight into neural connectivity defects associated with ASDs.

2-C-66 Molecular basis of using scyllo-inositol as a treatment for neuropsychiatric symptoms

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The endogenous stereoisomer scyllo-inositol is currently in clinical trials for treatment of neuropsychiatric symptoms in Alzheimer's disease patients. The current study investigates the interactions between scyllo-inositol and the molecular pathways implicated in neuropsychiatric symptoms. We hypothesize that lowered level of myo-inositol in the brain, an effect of scyllo-inositol treatment, alters inositol/calcium signaling resulting in modulation of CaMKII and PKC - major kinases in the brain and their downstream synaptic targets crucial in the regulation of neuropsychiatric symptoms. Using C56BL/6 mice, we fractionated three brain regions implicated in neuropsychiatric pathologies - hippocampus, striatum, and ventral mesencephalon, into subcellular fractions. Immunoblotting showed that in the hippocampus, scyllo-inositol treatment decreased expression of synaptic CaMKII and PSD-95. Phalloidin staining showed a corroborative decrease in the number of dendritic spines. The apparent loss of post-synaptic function was accompanied by an unexpected upregulation of pre-synaptic proteins including synaptophysin and alpha-synuclein. Most interestingly, the opposite results were observed in the striatum and the ventral mesencephalon. The regional specificity of scyllo-inositol treatment with regard to calcium-dependent kinases may thus explain its efficacy in treating region-specific dysregulations such as neuropsychiatric symptoms.

2-C-67 Characterization of functional and pathological changes in the brain microvasculature in a rat model of Alzheimer's disease

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Altered cerebral microvasculature in Alzheimer's disease (AD) may precede onset of clinical symptoms. Early detection of AD can be advanced through animal models that recapitulate more closely the vascular aspects of clinical AD. Our study examines the microvascular pathologies and changes in vascular function in the TgF344 rat model to assess the extent to which it replicates human AD pathology. ThioS and Methoxy-X04 stainings showed that in TgF344 rats, cortical parenchymal plaques concentrated in lateral-ventral regions while sparsely distributed in somatosensory and motor regions, and that perivascular Abeta pathologies appeared primarily in the arterioles of somatosensory cortex. Immunoblotting revealed that compared to non-transgenic rats, protein expression of markers for mural cell activity was increased in TgF344 rats while markers for blood-brain barrier integrity were unaltered. We employed in vivo two-photon fluorescent microscopy to image the microvessels of the primary somatosensory cortex in eliciting global vasodilation through CO2 challenge. Vascular reactivity of both arterioles and venules was significantly impaired in Tg rats such that the vascular response to CO2-induced increase in blood flow was attenuated. In conclusion, TgF344 rats captures several key phenotypes of vascular pathology in AD that enables investigation of functional changes in cerebral

microvasculature that are clinically relevant toward explaining the mechanism behind corresponding changes in human AD and eventually identifying early indicators of AD prior to its onset.

2-C-68 The role of hypertension and inflammation in an Alzheimer disease rat model

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Objective: Evaluate whether hypertension can trigger cognitive impairment, white matter inflammation, and β-amyloid (Aβ) related pathology in a transgenic mutant amyloid precursor protein (hAPP) rat model of Alzheimer disease (AD). Methods: Transgenic Fischer 344 rats overexpressing hAPP with Swedish and Indiana mutations received 8 weeks of continuous angiotensin II (Ang-II) infusion by subcutaneous osmotic minipump (n=15). Platform location learning and delayed match-sample testing in the Morris Water Maze assessed for impairments in learning, spatial-reference memory, and working memory. Brain tissue cross-sections were analyzed for inflammation using an antibody for activated microglia (OX6). Results: Elevated blood pressure impaired both wildtype and transgenic rats in the delayed match-sample task, with a trend of greater impairment in the transgenic group. Preliminary tissue analysis indicates that the transgenic groups have increased activation of microglia in white matter. Conclusions: Spontaneous neuropathology has not been previously reported in the transgenic strain, but increased microglia activation suggests the presence of abnormal white matter inflammation. White matter pathology may account for the greater cognitive effect that Ang-II infusion had on the transgenic group. Further work will be necessary to establish whether there is a pathological interaction between elevated blood pressure and overexpression of the mutant human amyloid precursor protein.

2-C-69 Inhibition of co-chaperone proteins to mitigate dopaminergic neurodegeneration

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The Bcl2-associated athanogene (BAG) family of co-chaperones regulates components of the chaperone and ubiquitin-proteasome systems, including Hsp70, a chaperone protein shown to be protective in models of Parkinson's disease (PD). BAG family proteins also interact with several key molecules implicated in PD pathogenesis, such as parkin, LRRK2, and PINK1. Overexpression of certain BAG family proteins can enhance alpha-synuclein (aSyn) aggregation and dopaminergic cell death in vivo. Hypothesis: targeted knockdown of BAG family proteins will simultaneously impact several relevant PD targets and thereby modulate the formation of aSyn oligomers and dopaminergic neuron survival. Three short hairpin RNA (shRNA) constructs that specifically and efficiently knock down rat BAG proteins were identified by in vitro screening, and then packaged into AAV1/2 vectors co-expressing GFP. These vectors were intranigrally injected to female Sprague-Dawley rats to characterize AAV expression pattern and degree of knockdown. AAV-shRNAs were similarly administered in two rat models of Parkinson's disease: targeted overexpression of human A53T aSyn (A53T-aSyn) and medial forebrain bundle axotomy (MFBx). In the A53T-aSyn model, forepaw asymmetry was evaluated using the cylinder test at 3 and 6-weeks post-injection. In both models, substantia nigra-containing sections were stained to examine dopaminergic cell survival and activation of cell death pathways. Preliminary results show AAV-shRNA treatment modulates activation of cell death pathways and dopaminergic cell survival.

2-C-70 Abeta Intermediates in the CSF of Patients with Mild Cognitive Impairment versus Alzheimer Disease

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An imbalance between production and clearance of Amyloidβ (Aβ) might be key to start the pathological cascade of Alzheimer disease (AD). While Aβ is a heterogeneous mixture of peptides with different solubilities, oligomeric states and toxic properties, especially Aβ42 is believed to be the main culprit in AD. A variety of enzymes (neprilysin 1/2, insulin-degrading enzyme, endothelin-converting enzyme, BACE1/2) degrade and convert Aβ into less-toxic intermediates. Aβ34, such an intermediate, is proteolytically generated by γ-secretase followed either by β-secretase 1 (BACE1) or its close homolog BACE2. By studying Aβ catabolism in patients with mild cognitive impairment (MCI) and AD, we now begin to understand the differences in enzymatic Aβ clearance in early stages of AD compared to later stages. We generated several monoclonal antibodies against Aβ fragments detected in human CSF. The specificity and avidity of the neoepitope specific antibodies were verified by surface plasmon resonance and immunoassays. Cerebrospinal fluid (CSF) from patients with non-AD/MCI, MCI and AD was received from the Clinic at the Division of Psychiatry, Zurich and VU Medical Center, Amsterdam. We found Aβ34 significantly elevated in CSF samples of individuals with MCI compared to those from non-AD and AD. This suggests that during MCI, there is an elevated enzymatic Aβ-clearance activity, indicated by a transient increase of the specific fragment Aβ34. We propose that enzymatic clearance might be enhanced early in AD and return to normal with the progress of the pathogenesis.

2-C-71 Interleukin-4-evoked alternative microglial activation increases neutrophil infiltration, astrogliosis and neuron damage if injected into the brain at the onset of ischemia

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After stroke, the CNS undergoes a prolonged inflammatory response that involves primarily three innate immune cell types: resident microglia, and blood-derived macrophages and neutrophils. Microglia and macrophages can undergo complex activation processes. These range from potentially cytotoxic, pro-inflammatory responses to alternative activation, which is thought to reduce inflammation and promote repair. We tested the hypothesis that boosting alternative activation at the onset of ischemia will be beneficial. Endothelin-1 was stereotaxically injected into the rat striatum to cause transient focal ischemia, with or without IL-4. We quantified several aspects of inflammation, as well as glial responses and neural damage from 1 to 7 days. Within the infarct, IL-4 increased transcript levels of several genes associated with alternative activation, but had little effect on pro-inflammatory mediators. Surprisingly, IL-4 modestly increased neurodegeneration at 1 day, while having little effect on the extent of white matter injury. Increased neurodegeneration coincided with increased numbers of CD206+ and CD68+ microglia/macrophages, and increased neutrophil infiltration. At 7 days, IL-4-treated rats had more microglia/macrophages in the ischemic infarct, and more pronounced astrogliosis in the surrounding ipsilateral striatum. Together, our results suggest that skewing the brain to an anti-inflammatory state at the onset of ischemia might be initially detrimental. The enhanced alternative activation of microglia/macrophages will need to be studied further.

2-C-72 Compensatory forelimb opportunity affects performance in a rat model of post-stroke reaching.

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The Montoya staircase is a sensitive and efficient method for measuring skilled forelimb reaching; however, little is known about how compensatory movement affects performance in this apparatus. In previous studies, we noticed rats' post-stroke reaching performance "plateaus" at around 1 month post-stroke, and hypothesized that performance may increase given more space to perform the reaching task. Here, reaching performance was assessed in staircase apparatuses of varying dimensions, providing different movement opportunities. Male Sprague Dawley rats underwent forelimb cortex stroke using endothelin-1, resulting in persistent forelimb deficits in staircase ($p<0.001$) and other tests. Animals were tested in standard staircases until individual performance plateaued, and then were switched into larger staircases for additional testing. Reaching performance immediately increased upon switching to larger staircases in a subset of animals, followed by a re-establishment of performance plateau. Regression analyses revealed that the level of initial impairment significantly predicted the magnitude of benefit that animals experienced when switched into larger staircases ($p=0.003$), while body mass, injury size, and week of switching did not. Kinematic analyses are in progress to compare and quantify movements in both standard and large staircases. Our data further support the importance of careful dissection of movement strategies (i.e. compensation vs recovery) in preclinical studies of functional recovery.

2-C-73 Neuronal nitric oxide synthase regulates the slow EPSC of cerebellar PF-PN synapses by modulating STIM1-mediated gating of TRPC3 channels

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Studies have shown that neuronal nitric oxide synthase (nNOS) is highly expressed in cerebellar parallel fiber and the nNOS-produced NO critically regulates the transmission and plasticity of the parallel fiber-Purkinje neuron (PF-PN) synapses. The mGluR1-initiated slow EPSC at the cerebellar PF-PN synapse is mediated through the Ca2 permeable TRPC3 channels, which are controlled by interactions with stromal interaction molecule 1 (STIM1). We explored the role of nNOS-NO signaling in the regulation of slow EPSCs and the underlying mechanism. The amplitude of slow EPSCs in nNOS-/- mice was significantly larger than that in wild type (WT) mice. A voltage-ramp applied to PNs isolated from WT and nNOS-/- mice revealed a transmembrane current that was enhanced by the mGluR1 agonist DHPG and reduced by the TRPC3 inhibitor Pyr3, indicating a TRPC3-mediated conductance. The amplitude of TRPC3 currents was larger in nNOS-/- PNs than that in WT PNs and it was significantly reduced by the NO-donor GSNO. A pyr3-senstive conductance was detected in HEK293 cells transfected with cDNAs of TRPC3 and STIM1. GSNO significantly reduced the pyr3-senstive conductance in cells transfected with STIM1, but not in cells transfected with a STIM1 mutant (Cys49Ser and Cys56Ser). Our results suggest that nNOS-NO down-regulates slow EPSCs at cerebellar PF-PN synapses possibly by S-nitrosylation of STIM1.

2-C-74 Vasculotide treatment accelerates restoration of the blood-brain barrier after focused ultrasound in a mouse model of Alzheimer's disease

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Focused ultrasound (FUS), in presence of microbubbles, transiently induces blood-brain barrier (BBB) permeability to allow for minimally invasive delivery of therapeutics, to targeted areas of the brain. Restoration of the BBB following FUS occurs rapidly in healthy models, however, the primary clinical use

would be in neurological disorders, such as Alzheimer's disease (AD), where BBB integrity may be compromised. The use of FUS to deliver AD therapeutics could have beneficial clinical implications, however, it is unknown whether the plasticity of the BBB and its capacity for repair is maintained in the presence of AD pathology. Furthermore, we sought to accelerate BBB restoration using Vasculotide (VT), a synthetic angiopoietin-1 mimetic that promotes vascular stability and reduces endothelial cell permeability. Using a transgenic (Tg) mouse model of amyloidosis and their non-Tg littermates, VT was injected, every 48 hours for 2-3 months. We used FUS to transiently induce BBB permeability, which was monitored by MRI and quantified at 6, 12 and 20 hours post-FUS. VT significantly accelerated BBB restoration, with no significant difference between Tg and non-Tg mice. VT also reduced the initial enhancement and acoustic pressure to induce BBB permeability, with no difference between Tg and non-Tg mice. Our research provides a better understanding of the effects of FUS, and is the first to examine the effects of VT on BBB permeability. This research presents a novel method of facilitating BBB closure that could lead to co-treatment of VT with FUS delivery of AD therapeutics.

2-C-75 Mobilization of Hematopoietic Precursor Cells Highly Expressing the Interleukin-1 Receptor to the Central Nervous System During Experimental Autoimmunce Encephalomyelitis

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Hematopoietic stem cells (HSCs) are the main source of the leukocytes forming the immune system and thus possess the capacity of reacting to inflammatory processes by generating the proper cell type. Our recent experiments have shown that Lin- Sca1+ CD34+ 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. EAE is actively induced by s.c. injections of MOG35-55 in WT mice and mice lacking either IL-1β or IL-1R1. To do so, we monitored and characterized the presence of HSCs or their progeny (effector cells) by immunofluorescence staining on tissue sections 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 and spleen of naïve and EAE mice. FC analysis of IL-1R1+ Lin- cell populations in the bone marrow revealed that these cells are HSCs and early multipotent progenitor cells (MMPs). Intravenous infusion of these cells 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 signaling by IL-1 in HSCs/MMPs might be of great relevance to EAE and MS. Future work will assess the importance of IL-1 signaling in IL-1R1+ HSCs/MMPs during EAE.

2-C-76 Examining the protective effects of physical exercise on the hippocampal formation in a mouse model of Alzheimers disease

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Neuronal and cerebrovascular function is highly interrelated in the central nervous system. A robust and healthy vascular network is required for normal neuronal development, maintenance and transmission. Neurovascular dysfunction constitutes an integral part of Alzheimer's disease (AD) pathology and greatly contributes to its progression. Accumulation of amyloid beta peptides (Aâ) alters cerebrovasculature

and induces neurotoxicity, resulting in cognitive impairment. Physical exercise is one of the most robust non-pharmacological stimulants of brain function, capable of circumventing cognitive deficits observed in AD. The present work examined the extent to which the brain is capable of adapting to or reversing Aâ-induced changes under running and sedentary conditions. We hypothesized that physical exercise supports memory function by maintaining normal vasculature and neurogenesis while stabilizing Aâ pathology in the TgCRND8 mouse model of amyloidosis. Our results indicate that in TgCRND8 mice running for one month, spatial memory was restored to non-transgenic levels, while exercise did not significantly affect neurogenesis or plaque burden. In TgCRND8 mice running for two months, spatial memory and neuronal maturation were improved and plaque load was diminished. Lastly, in transgenic mice running for 3 months, hippocampal vascular morphology was normalized, CAA was reduced, and spatial memory was preserved. In conclusion, this work suggests that physical exercise is an attractive treatment strategy capable of addressing AD pathologies. It provides evidence that physic

2-C-77 Identification of protein interactions regulated by alpha-synuclein serine 129 phosphorylation

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Our objective is to characterize novel protein interactions with alpha-synuclein (α-syn), the central protein in neurodegenerative disorders classified as synucleinopathies. Over 90% of aggregated α-syn is phosphorylated at the serine 129 position, compared to 5% in healthy controls, suggesting phosphorylation is involved in α-syn pathology. To assess the effects of α-syn phosphorylation, an α-syn interaction screen was performed using synaptosomes obtained from B6129x1-Snca tmlRos1/J α-syn knockout mice. These lysates were eluted through columns containing agarose beads cross-linked to either phosphorylated or non-phosphorylated wild-type human α-syn. Proteins bound specifically to the column were eluted then analyzed by mass spectrometry to yield a list of potential interacting proteins. Using these preliminary results a candidate protein was selected; protein kinase C and casein substrate in neurons 1 (PACSIN1) is a presynaptic protein involved in synaptic vesicle endocytosis. We tested whether over-expressed or endogenous PACSIN1 co-immunoprecipitated (coIP) with α-syn in cell lines and mouse brain synaptosomes. Despite evidence that PACSIN1 was retained on columns with covalently attached α-syn, it nevertheless failed to coIP with α-syn under resting or stimulated conditions. The high prevalence of phospho-Ser129 α-syn in disease pathology suggests it is related to protein aggregation. Examining proteins that interact with phospho-Ser129 α-syn may provide clues as to the role of α-syn phosphorylation in pathological conditions, leading to new therapeutic targets.

2-C-78 Neuroprotective Potentiel of Epsilon-Viniferin in a Cellular Model of Parkinson's Disease

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The polyphenol epsilon-viniferin (viniferin) is a dimer of resveratrol, a natural molecule well known for its anticancer, cardio-protective and anti-inflammatory effects. Several works suggest that viniferin owns, like resveratrol, antioxidant properties that can lower the production of reactive oxygen species (ROS), oxidative stress and cellular death. Currently, the neuroprotective potential of viniferin is far of being clearly investigated. According to recent discoveries, a decrease of oxidative stress can prevent the destruction of dopaminergic neurons, a characteristic feature of Parkinson's disease (PD). In this

context, the aim of our study was to evaluate the neuroprotective potential of the polyphenol viniferin in dopaminergic neurons, from NGF-differentiated PC12 cells, a cellular model of PD. The neuronal cells were pre-treated or not with resveratrol or viniferin or a mix of the two. Then, they were treated with the neurotoxin 6-hydroxydopamine (6-OHDA), known to induce Parkinsonism in rats. Cytotoxicity and the survival rate were quantified by colorimetric assay. Our results show that viniferin protects neuronal PC12 from 6-OHDA-induced cellular death and that a mix of resveratrol and viniferin can further protect neuronal cells from the toxic insult. We also studied the possible role of viniferin on the apoptotic cascade by assessing the protein expression levels of caspase-3 and PARP. Altogether, our data highlight a novel role for viniferin as a neuroprotective molecule in a dopaminergic cellular model of PD.

2-C-79 Behavioral and neurochemical changes in mice with increased dopamine transporter and decreased vesicular monoamine transporter 2 expression

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The dopamine system is heavily involved in motor control and response to rewarding drugs such as amphetamine. Two important proteins that contribute to dopamine signaling are the dopamine transporter (DAT) and vesicular monoamine transporter 2 (VMAT2). DAT takes up extracellular dopamine and VMAT2 stores dopamine into vesicles. We altered DAT and VMAT2 levels in transgenic mice to investigate the effects on dopamine homeostasis and dopamine-related behaviors. Specifically, DAT over-expressing (DATtg) mice were generated by BAC transgenesis and VMAT2 knockdown (VMAT2kd) mice were created by gene targeting. DATtg and VMAT2kd mice were interbred to produce DATtg/VMAT2kd mice that concurrently show increased DAT and decreased VMAT2 levels. Appropriate DAT and VMAT2 protein expression was confirmed in adult mice using western blots. In comparison to other genotypes, DATtg/VMAT2kd mice are smaller and show reduced survival. Striatal dopamine tissue content is drastically low in these mice, while metabolite to dopamine ratios are increased. Basally, DATtg/VMAT2kd mice display locomotor hyperactivity. In response to low doses of amphetamine (0.5 and 1 mg/kg), they show enhanced locomotion and stereotypy versus wildtype mice. However, at 2 mg/kg of amphetamine, they display abnormal involuntary movements (jerking, tremor) suggesting hypersensitivity to the effects of amphetamine. Overall, DATtg/VMAT2kd mice show changes in dopamine levels, basal motor behavior and amphetamine response, highlighting the importance of DAT and VMAT2 in maintaining dopamine homeostasis and function.

2-C-80 High-throughput phenotypic profiling of genes implicated in Autism Spectrum Disorders

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A major challenge to finding the causes of Autism Spectrum Disorders (ASD) is that thousands of gene mutations have been linked to the disease. Finding causal links between mutations and symptoms requires a system in which we can rapidly manipulate genetic variation and measure the resulting phenotype. One endophenotype found in ASD is disrupted habituation. Habituation is a form of learning observed as a decrease in responding to repeated stimulation. Habituation has been conserved through evolution, making it amenable to study using genetic model organisms such as Caenorhabditis elegans. Here, we use a machine vision system, the multi-worm tracker, to assay mechanosensory habituation in 52 strains of C. elegans each carrying a mutation in an ortholog of an ASD-linked gene to determine

which genes disrupt habituation when mutated. Our screen identified several habituation mutants from the ASD-linked genes; these genes fall into three main functional groups: cell-adhesion molecules, ion channels, and transcription factors. Of note, CTNNB1(bar-1), FAT3(cdh-4), and CREBBP(cbp-1) mutants all showed decreased habituation across multiple behavioural measures. Rescuing C. elegans disrupted habituation phenotypes with orthologous human genes will confirm functional homology between C. elegans and human genes. If the human gene rescues the worm phenotype we can then rescue with human variants found in ASD and categorize them in to variants that rescue and those that do not. This will allow us to group variants into functional categories that may shed light on their role in ASD.

2-C-81 Are There Sex Linked Differences Following Ischemic Injury Across the Longitudinal Axis of the Rat Hippocampus?

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Ischemic stroke is characterized by a reduction of cerebral blood flow that causes an insufficient supply of oxygen and nutrients to neurons. Despite being the third leading cause of death and a major cause of disability among Canadians, the ability to treat stroke is limited, in part due to an incomplete understanding of the factors that may guide cell death. For example, previous work has suggested that the response to brain injury may differ between male and female brain. As well, not all brain areas are equally affected by ischemia; for instance, the hippocampus (HP) is highly vulnerable to such injury, and some areas of the structure may be more sensitive than others. As a result, our research aims to investigate fundamental factors that may influence variability in response to neuronal injury. To determine whether susceptibility to ischemic insult is affected by either sex, or hippocampal region, oxygen-glucose deprivation (OGD; an in vitro model of stroke) will be applied to tissue slices prepared from the septal and temporal poles of male and female Sprague-Dawley rats. Cell viability assays, which measure mitochondrial activity (TTC metabolism) and cell membrane integrity (LDH release), will be used to compare post-OGD slice viability. We predict that both regional and sex-linked differences will be observed. By examining basic variables that may explain differences in tissue response to ischemic insult, we hope to enhance our ability to design pharmacotherapies to treat brain injury.

2-C-82 A novel chemo-optogenetic model of inducible focal epileptic seizures

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Epilepsy is a common neurological disorder, manifested by synchronized neuronal seizures that can rapidly spread to remote brain regions. However, studies of epileptic seizures in animal models are limited due to the lack of focal epilepsy models in which seizures can be reliably induced. We developed a novel chemo-optogenetic model that enables light-inducible seizures at a defined cortical locus. This was achieved by co-expressing an engineered inhibitory receptor (hM4D) along with channelrhodopsin in GABAergic interneurons (INs) of the medial prefrontal cortex, by stereotactically injecting adeno-associated virus to GAD2-Cre transgenic mice. Seizure activity was monitored by in vivo EEG recording synchronized with camera imaging. Systemic application of the synthetic ligand (CNO) silences these neurons, thereby causing an initial seizure, as expected by silencing of inhibition. After this initial seizure, brief light activation of these same neurons paradoxically induces reproducible focal seizures. Systemic pre-treatment of mice with NKCC1 transporter blocker Bumetanide eliminated the induction of seizure activity by light. These paradoxically induced seizures might therefore be explained by changes in

the reversal potential of GABA, as a result of re-expression of the NKCC1 transporter, which is not expressed in the healthy adult brain. With this model we will be able to investigate many aspects of epileptic seizures in vivo, such as their spatiotemporal progression, local circuit rearrangements, and changes in the balance between excitation and inhibition.

2-C-83 The role of the subthalamic nucleus in response inhibition: evidence from both single-cell level and local field potentials in the human sub-thalamic nucleus with Parkinson's disease

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Deep brain stimulation (DBS) of the sub-thalamic nucleus (STN) is an effective treatment of motor symptoms (akinesia, bradykinesia, tremor) in Parkinson's disease (PD) patients. Several studies support the role of STN in inhibitory and executive motor control. According to the previous studies, it was hypothesized that firing rates of single-cell STN neuron were higher after NO-GO trials rather than GO trials, because of its essential roles in inhibitory motor functions. A GO NO-GO reaction times task was then carried out to determine the activity of STN in response to GO (n=20) and NO-GO (n=20) visual stimuli. The GO cue used was a picture of a rabbit and the NO-GO cue was the same picture with a large red "X" cross on it. The GO-NOGO trial then compared to a trial that only has GO cues to differentiate better the GO trials embedded in the GO-NOGO block. Data were collected from awake patients undergoing bilateral DBS-STN implantation surgery. The firing rates of STN single-cell neuron were recorded using two microelectrodes initially 600 µm apart in each side. Results then analyzed using stimulus histogram tools in Spike2 (CED) and Local Field Potential (LFP) beta oscillations. Although more data needs to be collected, the preliminary findings of a tonic inhibitory response during the whole trial and phasic GO responses indicate STN involvement in motor inhibition control and generation of voluntary movements respectively.

2-C-84 Multi-drug therapeutic approach enhances neurogenesis in Alzheimer's disease mice

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Single drug treatments for Alzheimer's disease (AD) have had limited success in the clinic, and yet despite the need for multi-drug therapies there are few preclinical proof of concept studies. Targeting amyloid and growth factor deficits, we present a novel combination therapy which promotes hippocampal neurogenesis in AD. TgCRND8 AD mice and non-transgenic littermates were treated with scyllo-inositol or untreated. Another cohort of TgCRND8 mice were treated with scyllo-inositol, neotrofin or a scyllo-inositol/neotrofin combination. All mice were injected with bromodeoxyuridine to label replicating cells. scyllo-Inositol treatment, to reduce amyloid, reversed hippocampal neurogenesis deficits in TgCRND8 mice with early AD-like pathology. However, in older TgCRND8 mice with established AD-like pathology, scyllo-inositol treatment reduced amyloid load without altering deficits in neurogenesis. We hypothesized that amyloid buildup damages the hippocampal neurotrophic niche, rendering amyloid-targeted therapies insufficient. We, therefore, combined scyllo-inositol with neotrofin to promote neurotrophin signaling. While neotrofin alone did have effects on hippocampal neurogenesis in TgCRND8 mice with established AD-like pathology, when combined with scyllo-inositol neuronal survival/differentiation was enhanced. Since hippocampal neurogenesis is dysfunctional in AD it likely contributes to behavioural symptoms. We propose this proof of concept for the novel

combination treatment targeting amyloid toxicity and neurotrophin deficits as a promising AD therapeutic paradigm.

2-C-85 Intellectual Outcome in Molecular Subgroups of Medulloblastoma

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Medulloblastoma is a heterogeneous disease comprised of four molecular subgroups (WNT, SHH, Group 3 & Group 4) with distinct demographic, genetic and clinical features; however, their intellectual outcomes are unknown. The goal of the present study was to characterize intellectual functioning in each subgroup, and to evaluate the implications of limiting radiation exposure. 121 patients with medulloblastoma (51 Group 4; 25 Group 3; 28 SHH; 17 WNT), treated at the Hospital for Sick Children (Toronto, Canada), Children's National Health System (Washington, DC) or the Lucile Packard Children's Hospital (Palo Alto, CA), had intellectual assessments. First, we compared intellectual trajectories between subgroups. Next, we evaluated the effect of treatment with reduced-dose radiation plus a tumor bed (TB) boost vs. treatments that deliver higher radiation doses and/or larger boost volumes to the brain ('all-other-treatments') within subgroups. Linear mixed modeling was used to determine the change in intelligence scores over time. We found that intellectual outcomes declined comparably in each subgroup except processing speed; SHH declined less than Groups 3 & 4 (all $P<0.05$). SHH had the lowest incidence of cerebellar mutism and motor deficits. Treatment with reduced-dose CSI TB boost was associated with preserved intellectual functioning in patients with good prognosis (i.e., WNT & Group 4 together) only. SHH patients appear to have the most distinct functional and processing speed outcomes, and only WNT & Group 4 patients seem to benefit from limiting radiation exposure.

2-C-86 Disruption of TAO2 in Autism Spectrum Disorders and the Characterization of TAO2 KO Mice as an ASD Model

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Atypical brain connectivity is a major cause for pathophysiology of Autism Spectrum Disorders (ASDs). The thousand and one amino acid kinase 2 (TAO2) plays a major role in neuron development and was first discovered in a common ASD associated microdeletion region, 16p11.2. To study the underlying pathophysiology of ASDs we are using a TAO2 KO mouse model. Initial studies revealed a gross reduction in cortex size, accompanied by behavioural deficits seen in many ASD animal models, including reduced social interaction, increased anxiety, and alteration in memory formation and learning. Cortical neurons in TAO2 KO mice had reduced dendritic arborization, overall spine number, and a shift towards more immature dendritic spines. The deficits in brain connectivity are corroborated using electrophysiology, and explain the observed in ASD-like behaviour. Concurrently, exome and whole genome sequencing of families with at least one ASD proband identified multiple rare-inherited variants and 2 de novo variants in the TAO2 gene. Overexpression of the 2 de novo variants in cortical neurons reveal altered dendrite morphology and both variants have altered functionality measured by

phosphorylation of downstream targets (JNK and p38). The identification of 2 functionally validated de novo mutations in TAO2 highlights the significant impact disruption of TAO2 has in the pathophysiology of ASDs. By using our TAO2 KO mice model we can now identify therapeutic drug targets and test their ability to rescue the ASD-associated behavioural and morphological deficits.

2-C-87 Neuroprotective and Immunomodulatory Effects of the Plasmalogens Precursor, PPI-1011, in the Enteric Nervous System in Parkinson's Disease

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SYNOPSIS: Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide. It is characterized by motor symptoms originating from the degeneration of nigrostriatal dopaminergic (DA) neurons. Early stages of PD have been associated with an alteration in dopamine production in intestinal DA neurons accompanied by inflammation. Interestingly, decreased serum concentrations of a particular type of glycerophospholipids - plasmalogens (PLS) - have been reported in PD patients. PLS play numerous roles in membrane structure mediated functions such as free radical scavenging and neurotransmitter release, highlighting a potential therapeutic interest. OBJECTIVE: The present study evaluated the neuroprotective and anti-inflammatory properties of a PLS precursor, PPI-1011, in the intestine of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice. RESULTS: C57BL/6 male mice were treated by gavage for 10 days with PPI-1011 (10 and 50 mg/kg). On day 5, mice received 4 i.p. injections every 2 hours with either saline or the neurotoxin MPTP (5.5 mg/kg) to model PD. In MPTP-treated mice, PPI-1011 prevented the loss of tyrosine hydroxylase expression and reduced the infiltration of macrophages in the myenteric plexus, suggesting that PPI-1011 has neuroprotective and anti-inflammatory properties in the gut. CONCLUSION: PPI-1011 could possibly be considered as a prophylactic nutraceutical treatment for early PD.

2-C-88 GABA and glutamate levels in the brains of people with multiple sclerosis are related to markers of demyelination and clinical impairment

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Background: While converging lines of evidence support the involvement of glutamate (Glu) and γ-aminobutyric acid (GABA) in neurological disease, further research in humans is needed to understand the clinical impact of neurotransmitter alterations. Objective: Among people with multiple sclerosis (MS), we assessed the extent to which regional Glu and GABA concentrations are related to structural brain damage and clinical impairment. Methods: Twenty-one healthy individuals and 48 people with MS participated (all right-handed). Fine motor impairment was assessed with the 9-hole Peg Test. Proton magnetic resonance spectroscopy (1H-MRS) data were acquired from sensorimotor and parietal regions of the brains' left cerebral hemisphere. LCModel software was used to quantify GABA, Glu, macromolecules (MM), and N-acetyl-aspartate (NAA), which were corrected for relaxation and partial volume effects, and age. Magnetization transfer ratio (MTR) was measured to provide a marker of myelin integrity. Results: Compared to healthy controls, Glu, NAA, and MM concentrations were lower in the MS group (ps < 0.05). When adjusting for anxiety and depression, MS participants had higher sensorimotor GABA concentration (p < 0.05). Lower regional MTR was linked to NAA, MM, Glu, and

GABA abnormalities. Lower sensorimotor NAA and GABA concentration were independent predictors of worse motor impairment (ps < 0.01). Conclusions: Demyelination may influence GABA and Glu concentrations. Regional alterations in GABA levels are related to motor impairment independently of structural brain damage.

2-C-89 Brain state dependent signaling and function of CRF1 receptors

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Anxiety and stress increase the frequency of epileptic seizures. Here we show in a rat model of temporal lobe epilepsy corticotropin releasing factor (CRF) increased excitability of the piriform cortex (PC). In contrast to its action in normal PC where it dampened excitability. After seizure induction, CRF signaling occurs through a GPCR pathway involving Gs, whereas CRF activity was mediated through Gq/11 in non-kindled animals. This change in signaling is appeared to be mediated by the reduced expression of Regulator of G-protein Signaling protein-2 (RGS2). We also show RGS2 knock out mice have CRF responses identical to epileptic rats. These observations indicate that brain pathological state may mediate the increased severity or contribute to co-morbidities of the underlying neurological disorders.

2-C-90 TrkB Activation Rescues PI3K/Akt Signaling and Autistic-Like Behavior in the Valproic Acid-Induced Mouse Model

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The molecular mechanisms underlying autistic behavior remain to be elucidated. We previously demonstrated reduced TrkB/Akt/mTOR protein and signaling in human idiopathic autism and in the valproic acid (VPA) rodent model. This evidence implicates defective TrkB/Akt/mTOR as a molecular substrate of autistic behavior and a potential therapeutic target for autism. Hence, we examined whether treatment with the partial TrkB agonist LM22A-4 would restore TrkB/Akt/mTOR signaling and ameliorate autistic-like behavior in mice prenatally exposed to VPA. Pregnant females received a single intraperitoneal (i.p.) injection of 500 mg/kg VPA on gestational day 12.5, while controls were injected with saline. Pups were weaned on postnatal day (PD) 21 and received an i.p. injection of either saline or LM22A-4 (0.05 mg/g) once daily from PDs 21-35. Sociability and repetitive digging were evaluated on PDs 29-34 using the three-chambered social approach task and marble-burying test, respectively. Litters were killed and brain tissue harvested on PD 35. Akt total protein and phosphorylation levels were measured by Western blotting. Behavioral results were dependent on sex, with VPA females lacking sociability and VPA males showing increased repetitive digging. Both VPA females and males had decreased phosphorylated Akt. LM22A-4 restored sociability, decreased repetitive behavior and rescued Akt phosphorylation. Our results corroborate the hypothesis that reduced TrkB/Akt/mTOR contributes to autistic behavior and that TrkB activation might have a therapeutic role in treating idiopathic autism

2-C-91 Quantitating Neuropathological Features in the Cerebellum of a Mouse Model of Fragile X Syndrome

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Fragile X syndrome (FXS) is a neurodevelopmental disorder on the autism spectrum caused by suppression of Fragile X Mental Retardation Protein expression coded for by the FMR1 gene. Human patients with FXS demonstrate hyperactivity, repetitive behaviors, intellectual impairments, and social/communicative deficits. The Fmr1 knockout (Fmr1-KO) mouse model of FXS displays many phenotypic similarities to the human syndrome. Cerebellar Purkinje cells are the sole output neurons of the cerebellum. These cells control motor function, vocalization and language comprehension, and cognition. A preliminary report of human FXS patients suggested Purkinje cell loss. However, anatomical information on Purkinje cells of the cerebellum in Fmr1 KO mice is not currently available. We hypothesize that Purkinje cells may be decreased in Fmr1 KO mice. To test this hypothesis, accurate quantification of Purkinje cells is crucial. However, it is difficult to obtain precise structural information on Purkinje cells due to the complex folded structure of the multiple cerebellar lobes. To solve this problem we are investigating CLARITY-based Purkinje cell detection in combination with the use of light sheet microscopy, to allow for quantification of Purkinje cells in the whole, intact cerebellum. Although the focus of our current study is FXS, we hope that the principles and technical details established here might be generally transferable to other mental disorders that exhibit Purkinje cell loss.

2-C-92 Characterizing the Effects of CBD in the Mesolimbic Dopamine System

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Emerging evidence suggests that cannabidiol (CBD) may interact with the mesolimbic dopamine (DA) system. The underlying neuroanatomical, neuronal and pharmacological substrates responsible for CBD's effects within the mesolimbic pathway, however, are not understood. Using a combination of in vivo electrophysiological recording and fear conditioning, the present study aimed to characterize the behavioural and pharmacological effects of CBD within the mesolimbic pathway, focusing on the nucleus accumbens shell (NASh) and ventral tegmental area (VTA). Associative fear memory formation was blocked by intra-NASh CBD. These behavioural effects were challenged with both DAergic and serotoninergic (5-HT1A and 5-HT1B) signalling blockade but only 5-HT1A blockade restored associative fear memory formation. In vivo intra-VTA electrophysiological recordings revealed that behaviourally effective doses of intra-NASh CBD elicited a predominant decrease in spontaneous DAergic neuronal frequency and bursting activity. These neuronal effects were bi-directionally modulated by co-administration of either 5-HT1A or DA receptor antagonists. Finally we demonstrated that administration of GABA A/B antagonists in the VTA followed by intra-NASh CBD restored associative fear memory formation. Our findings demonstrate a novel NAc-VTA circuit responsible for the behavioural effects of CBD via functional interactions with serotonergic and DAergic signalling substrates in the mesolimbic pathway.

2-C-93 Gait disturbances in the 5xFAD transgenic mouse model of Alzheimer's Disease

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Alzheimer's Disease (AD) is a disabling chronic disorder characterized by progressive cognitive impairment. However, patients may also experience gait disturbances. Given the high prevalence and poor prognosis of AD, the characterization of animal models for AD with face validity reproducing cognitive and non-cognitive disturbances of AD is important. However, whether gait disturbance is

reproduced in a mouse model of AD amyloidosis is not clear. We hypothesize that similar to AD affected individuals, the pathological aggressive 5xFAD mouse line will develop an age-dependent motor phenotype - particularly disturbances in gait parameters. Fourteen month old male 5xFAD mice and wild-type controls with the same genetic background were subjected to grip and locomotor tests. They were also subjected to gait assessments using the CatWalk automated gait analysis system. 5xFAD mice demonstrate deficits in motor coordination and speed. In addition to previously reported cognitive impairments, 5xFAD mice also demonstrate disturbances in gait, which is observed in patients throughout all stages of AD. The assessment of gait impairments in mouse models is highly relevant, as it can influence the results of behavioural analyses, and it could also serve as an endpoint for testing potential therapeutics for non-cognitive symptoms.

D – Sensory and Motor Systems

2-D-94 Activation of a Respiratory Medullary Motor Circuit by Remote Control

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Introduction: Reductions in tongue muscle tone can precipitate obstructive sleep apnea (OSA). The hypoglossal motor nucleus (HMN) is the source of motor output to the tongue, and pharmacological activation of the HMN may increase tongue activity and reduce OSA. However, there is no pharmacological agent currently able to selectively manipulate a channel that is restricted in its expression to the cranial motor pools. To identify the feasibility of pursuing such a "druggable" target at the HMN, we introduced "designer" receptors into the HMN and selectively modulated them with a "designer" drug. Methods: Hypoglossal motoneurons of ChAT-Cre mice (n=6) were transduced with activating receptors. After being instrumented for sleep and respiratory muscle recordings, mice were studied before and after intraperitoneal injection of vehicle and clozapine-N-oxide (CNO): CNO activates hM3Dq receptors but is otherwise biologically inert. Histology confirmed effective trans-gene expression at the HMN. Results: Systemic injection of CNO selectively increased tonic tongue muscle activity across all sleep-wake states (p=0.015). Tongue muscle activity was increased in non-REM and REM sleep by 385% and 273% (89.6% and 49.5% of normal waking values) respectively. Conclusions: Selective activation of a "designer" pharmacological target that is locally expressed in the HMN results in sustained reactivation of tongue muscle tone throughout sleep. This result establishes proof of principle for pursuing a restricted "druggable" target at the HMN as a potential pharmacotherapy for OSA.

2-D-95 Dynamic neural tuning and perception enables adaptation to natural sensory stimuli under behaviorally-relevant contexts

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It is generally assumed that the nervous system efficiently encodes sensory input by adapting its coding strategies to the constantly changing statistics of natural stimuli. However, the underlying mechanisms and their impact on perception and behavior remain poorly understood to this day. Here we investigated whether and, if so, how the weakly electric fish Apteronotus leptorhynchus adapt to the changing natural statistics encountered in their environment. These fish constitute an excellent model system for studying these important questions as our previous work has shown that SK channels are

adjusted such that sensory pyramidal neurons efficiently encode natural sensory stimuli, thereby leading to a match between behavior and natural scene statistics. Here we instead asked whether these fish could adapt to changes in natural scene statistics and, if so, what were the underlying neural mechanisms. To do so, we exposed the animal to stimuli whose statistics deviated from natural ones and tested behavioral responses. Our results show that behavior gradually changed in order to match the new stimulus statistics. Recordings from sensory neurons revealed that these progressively changed their tuning properties in order to efficiently encode these new stimuli. It is likely that these changes in tuning are caused by differing levels of expression of SK channels. Our results thus uncovers generic mechanisms underlying adaptive coding and consequences on perception of stimuli with different statistics that are likely to be shared across sensory systems and across species.

2-D-96 Interactions between Posterior Parietal and Primary Motor Cortices relates to Rubber Hand Illusion

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Background: Although enhanced multi-modal sensory integration(SI)s have been suggested in older people as a compensation of ageing in behavioral studies, how ageing affects the neural underpinnings for multi-modal SI, particularly posterior parietal cortex (PPC)-primary motor cortex (M1) interaction, remains unclear. We compared older and young adults regarding the level of visuo-tactile-proprioceptive integration evoked by rubber hand illusion (RHI) and its modulation of the PPC-M1 interaction. Hypotheses: PPC-M1 interaction will be modulated during RHI. Older subjects will show enhanced RHI and stronger modulation of PPC-M1 interaction by RHI compared to young adults. Methods: We tested 13 healthy young and 13 older adults. Multi-modal SI was induced and assessed by the RHI paradigm in which a rubber hand in view and participant's occluded own hand were being stroked simultaneously. Before and immediately after the induction, the PPC-M1 interaction was evaluated by using paired-pulse transcranial magnetic stimulation with conditioning stimulus to the PPC before test stimulus to M1 and recording motor evoked potentials from hand muscles. Results: The comparison between the two groups showed no significant differences in the level of RHI and its modulation of the PPC-M1 interaction. However, stronger RHI correlated with greater inhibitory PPC-M1 interaction during RHI. Conclusions: The correlation between stronger RHI and greater inhibitory PPC-M1 interaction suggests that PPC-M1 interaction is involved in mediating RHI. However, this interaction was not changed by ageing.

2-D-97 Subcortical encoding of speech cues in children with attention deficit hyperactivity disorder

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Introduction: There is little information about processing of nonspeech and speech stimuli at the subcortical level in individuals with attention deficit hyperactivity disorder (ADHD). The auditory brainstem response (ABR) provides information about the function of the auditory brainstem pathways. We aim to investigate the subcortical function in neural encoding of click and speech stimuli in children

with ADHD. Methods: The subjects include 50 children with ADHD and 34 typically developing (TD) children between the ages of 8 and 12 years. Click ABR (cABR) and speech ABR (sABR) with 40 ms synthetic /da/ syllable stimulus were recorded. Results: Latencies of cABR in waves of III and V and duration of V-Vn ($P \leq 0.027$), and latencies of sABR in waves A, D, E, F and O and duration of V-A ($P \leq 0.034$) were significantly longer in children with ADHD than in TD children. There were no apparent differences in components the sustained frequency following response (FFR). Conclusions: We conclude that children with ADHD have deficits in temporal neural encoding of both click and speech stimuli. It seems that there is a common dysfunction in the processing of nonspeech and speech stimuli at the brainstem level in children with suspected ADHD.

2-D-98 Modulation Effects and Time Course of Target-Distractor Similarity on Saccade Curvatures

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According to the weighted average account, saccade curvatures are due to interactions between neural populations in the intermediate layers of the superior colliculus (SCi) encoding different eye movement vectors. We examined a critical prediction of this account: whether saccade curvatures are functionally related to the level of activation/inhibition elicited by distractors. Furthermore, we examined the time course of these competitive interactions. We created stimuli by conjoining individual line segments into holistic objects. The similarity between stimuli was manipulated by varying the number of individual line segments shared between stimuli. The relative similarity between two bilateral distractors and a target was systematically varied on a search task in which participants were required to saccade to the target. When distractors were equally similar, saccades deviations were not different from baseline, $z = -0.26$, $p = 0.798$. When one distractor was more similar, saccades curved away from it, $z = -3.11$, $p = 0.002$. This shift only occurred during the first 60% of the length of the saccade. There was also a linear relationship between relative similarity and saccade curvature, $F(1,2) = 21.82$, $p = 0.043$, $R2 = 0.92$. The current results suggest that SCi neural activity elicited by visual and cognitive factors functionally modulate saccade curvatures, which is consistent with the weighted average account. However, saccadic shifts ceases after 60% of the movement suggesting that saccadic motor control (e.g., SCi neural activity) transitions into a winner-take-all model.

2-D-99 Multisensory electrophysiology reveals overt and subthreshold non-auditory influences on dorsal auditory cortex

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It has been well-documented that the brain is capable of reorganizing following sensory loss in both blind and deaf individuals. While many examples of this cross-modal reorganization exist in the literature, the neural mechanisms underlying this plasticity are not well understood. Recently, enhanced visual motion detection capabilities in deaf animals were localized to an auditory cortical region in the cat: the dorsal zone (DZ). Because this region receives direct input from visual cortical regions in both hearing and deaf animals, the goal of the present experiment was to examine whether and how these inputs are capable of influencing neuronal activity in hearing animals. To achieve this, we examined multisensory processing in DZ at multiple scales of neuronal activity in 6 adult domestic cats. These techniques allowed for the detection of subthreshold non-auditory influences in a region of auditory

cortex previously thought unimodal. We show that visual and somatosensory stimulation can differentially modify specific epochs within the auditory response. Analysis of local field potentials (LFPs) corroborated these findings, demonstrating visual influences at the vast majority of recording sites, with somatosensory-evoked activity present to a lesser extent. These findings demonstrate that active visual and somatosensory inputs are present in hearing DZ, and have important implications for understanding the neural mechanisms underlying cross-modal plasticity.

2-D-100 Real-time in vivo plasticity of corticostriatal afferent activity during skill learning

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Dynamic changes in cortico-basal ganglia circuit function underlie action learning. How changes in discrete, connectivity-specified circuits manifest in vivo during such learning remains unknown. Using in vivo fiber photometry, we assessed real-time activity and plasticity of distinct cortical inputs to the striatum during motor skill learning. The genetically encoded calcium indicator, GCaMP6s, was virally expressed in excitatory cortical neurons in motor cortex (M1) or medial prefrontal cortex (mPFC) of mice. An optical fiber was implanted into dorsolateral striatum (DLS) of M1-injected mice to target sensorimotor inputs, and dorsomedial striatum (DMS) of mPFC-injected mice to target associative inputs. Activity-dependent fluorescent calcium dynamics were assessed in presynaptic elements of these inputs as a proxy for projection activity as mice were trained on the accelerating rotarod. Sensorimotor inputs were engaged during initial trials on the rotarod, and showed a progressive decrease in activity with training. In contrast, engagement of associative inputs was modest during initial trials, peaked during early learning, and rapidly diminished as performance was automatized. Somatic photometric recordings of DLS-projecting M1 neurons and DMS-projecting mPFC neurons revealed learning-related activity changes comparable to those seen in their respective presynaptic elements. Our work describes novel approaches to observe real-time activity dynamics in discrete corticostriatal inputs, and provides new insight into how cortico-basal ganglia circuits encode action learning.

2-D-101 Galvanic Vestibular Stimulation in Primates: Recording Vestibular Afferents during Transmastoid Stimulation

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An increasingly popular tool to activate the human vestibular system is galvanic vestibular stimulation (GVS), electrical stimulation between surface electrodes on the mastoid processes behind the ears. While GVS evokes vestibular-related responses such as ocular and postural responses, and virtual motion perception, the dynamics of the vestibular signals behind the GVS-evoked responses remain unknown. Although vestibular afferent responses have been recorded during electrical stimulation, these studies used stimulating electrodes implanted in the ear. Here, to better understand how transmastoid GVS affects vestibular nerve activity, we recorded vestibular afferent responses during GVS applied between surface electrodes on the mastoid processes of alert macaques. We found that GVS activates non-specifically all vestibular afferents, both semicircular canals and otoliths, with irregular afferents being more sensitive, consistent with prior studies. We show that during sinusoidal stimulation, otolith afferents, much like canal afferents, displayed an increase in both gain and phase lead as a function of frequency. Comparable frequency responses were observed during broadband noise stimulation, suggesting that afferents encode GVS linearly. Furthermore, afferent responses to

constant current GVS show the presence of a slower dynamic. Together, these results reveal the actual neural correlate of GVS activation on the vestibular system - a fundamental step into understanding the effect of this technology required to advance its clinical and biomedical applications.

2-D-102 Noise enables multiplexed coding of fast and slow signals through synchronous and asynchronous spiking

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The prodigious capacity of our brain to process information relies on efficient neural coding strategies. In engineered systems, bandwidth is often increased by simultaneously transmitting multiple signals through a single communication channel, i.e. multiplexing. We hypothesized that sets of neurons form multiplexed representations by using synchronous (Sync) and asynchronous (Async) spikes to encode fast and slow signals, respectively. To verify our hypothesis, we applied mixed fast and slow signals plus independent noise to sets of model neurons and rodent pyramidal cells. Spikes driven by slow signals were desynchronized by noise whereas spikes driven by fast signals remained synchronous. Sync and Async spikes yielded distinct spike-triggered averages (STAs). The original mixed signal was more accurately reconstructed by convolving Sync and Async spikes with their respective STAs (i.e. demultiplexing) than by treating all spikes as equivalent. Next, we used conductance-based models to fit linear-nonlinear (LN) rate models with one or two streams. Comparing fitted LN models across noise levels revealed how noise facilitates the formation of orthogonal representations by segregating the streams. Lastly, using a leaky integrate-and-fire model, we show how the interspersed rough and smooth features of the threshold produce Sync and Async spikes by intersecting a noisy membrane potential trajectory. Our results reveal that noise promotes multiplexing by enabling sets of neurons to separate their representation of fast and slow signals between Sync and Async spikes.

2-D-103 Effect of allocentric cues on primate gaze behaviour in a cue conflict task

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The visual system can remember the location of a peripheral target relative to the self (egocentric) or to an external landmark (allocentric). The relative influences of each reference frame have been examined for reach (Byrne & Crawford, J. Neurophysiol. 2010), but not for the gaze control system. Here, we utilized a cue conflict paradigm to assess the effect of allocentric cues on gaze behaviour in the rhesus monkey. One monkey was trained to maintain central fixation while a target was presented for 100ms along with an allocentric cue. After a 100ms delay, a mask was shown for 100ms during which the allocentric cue was displaced by 8°. After a second delay of 300-700ms, the fixation point extinguished, acting as a 'go' signal for a head-unrestrained saccade towards the remembered target. The monkey did not look toward the original target, but rather toward a point shifted partially toward a virtual target defined relative to shifted cue location (i.e., in allocentric coordinates). Overall, there was a significant ($P<0.01$) allocentric shift in gaze endpoints relative to controls (no cue displacement), with a mean gain of 0.27 (where 0 = no shift and 1.0 = complete shift). In addition, the cue had a significantly greater effect when it shifted away from the fixation point ($P<0.01$) and when it shifted towards the original target ($P<0.01$). These findings suggest that internal representations of gaze targets are weighted between egocentric and allocentric cues, and this weighting is further modulated by specific spatial parameters.

2-D-104 An adaptation-induced tactile spatial illusion: experimental demonstration and Bayesian modelling

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Following focal sensory adaptation, the perceived separation between stimuli that straddle the adapted region is often exaggerated. For instance, in the visual tilt aftereffect illusion, adaptation to tilted lines causes subsequently viewed lines with nearby orientations to be perceptually repelled from the adapted orientation. Repulsion illusions in the nonvisual senses have been less well studied. Here, we investigated whether adaptation induces a repulsion illusion in tactile spatial perception. In a two-interval forced choice task, participants compared the perceived separation between two-point stimuli applied on the forearms successively. Separation distance was constant on one arm (the reference) and varied on the other arm (the comparison). Vibration of the skin between the two reference points focally reduced tactile sensitivity (adaptation) and significantly increased the perceived separation between the reference points (repulsion illusion). The experimental results are predicted by a Bayesian perceptual model that decodes two-point distances based on simulated neuronal spike counts. The Bayesian model also suggests that, for the repulsion illusion to occur, the decoder must be unaware of the adaptation.

2-D-105 Encoding of gravity by the periphery and the central neurons during passive and active head tilt

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During daily activity, our sensory system is activated by self-generated and external events. We have previously shown that cerebellar output neurons and their target neurons in the vestibular nuclei robustly encode passive motion in the horizontal plane, while they are attenuated during comparable self-generated head motion. However, natural head movements are not restricted to one plane and there are situations where the brain has to cope with gravity. Gravity acts as a steady passive stimulus on the vestibular system and its consequences on movement may be unbended in the internal model. We tested whether a neural representation of gravity is included in the internal model used to differentiate between passive and active motion, so that the neuronal response to gravity would be attenuated. We studied neuronal responses of cerebellar output neurons (rostral Fastigial nuclei, rFN) and their target neurons in the vestibular nuclei in alert macaques during passive and active tilt. Responses related to active tilts were significantly attenuated (relative to passive tilt) in the vestibular nuclei neurons and in rFN (67 vs 74%, $p>0.05$). To test for the alternative that attenuation occurs in the periphery, vestibular afferent responses were also recorded. As previously shown in the horizontal plane, the afferents similarly encoded passive and active tilt. Our findings indicate that the neural coding of active self-motion requires an elegant computation of an internal model of gravity at the central level but such computation does not influence peripheral coding of self-motion.

2-D-106 Effects of enriched environment exposure on retinal and visual cortex functions

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Environmental factors such as climate, food availability, predator presence and social interactions influence the development and behaviour of living creatures. Studies have demonstrated that exposition

to an enriched environment promotes neuronal plasticity and loss of function recovery. In this study, we examined the impact of housing environmental conditions on retinal, and visual cortex functions. Control mice and mice that were exposed to an enriched environment (EE) from birth were compared. The enriched environment consisted in group housing in larger cages, containing several toys which were moved or replaced at regular intervals. The control mice were individually housed in standard cages, following weaning. Retinal function was assessed with ERG recordings under both scotopic and photopic conditions. Flash intensity-response curves of ERG components (a and b waves, oscillatory potentials) were obtained. Environmental housing conditions did not affect a wave amplitude under either scotopic or photopic conditions. On the other hand, when compared to the control group, the intensities-response curve for the b wave was shifted to the right for the EE group but only under scotopic conditions ($p<0.001$). Also, oscillatory potentials intensities-response curve of the EE group was shifted to the left under photopic conditions ($p<0.001$). Finally, brain optical imaging will be performed and the effects of environmental enrichment on primary visual cortex' contrast sensitivity and spatial frequency selectivity will be determined.

2-D-107 Functional plasticity in primary somatosensory cortex supports motor learning by observing

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An influential idea in neuroscience is that the sensory-motor system is activated during action observation. This idea has recently been extended to motor learning. Action observation promotes sensory-motor plasticity as well as motor and somatosensory behavioural changes. However, it is unclear how the brain maps visual information onto motor circuits for learning. Here we present two experiments testing the idea that the somatosensory system, and more specifically primary somatosensory cortex (S1), plays a direct role in motor learning by observing. In Experiment 1 we applied nerve stimulation to either arm while subjects observed a tutor performing a force field learning task using the right arm. Stimulation occupied somatosensory cortical processing with unrelated input during observation. Stimulation delivered to the right arm (same arm used by the tutor) disrupted learning whereas left (opposite) arm stimulation did not. This suggests that a somatosensory representation of the observed effector is necessary, and hence must be unoccupied, for motor learning by observing to occur. In Experiment 2 we assessed changes in primary somatosensory (S1) cortical processing following motor learning by observing by measuring somatosensory evoked potentials (SEPs). The N20-P25 component, which is generated by S1, increased in amplitude only in subjects who observed the tutor learning. Moreover, SEP increases were correlated with subjects' subsequent behavioural motor learning scores. These experiments demonstrate that the somatosensory system supports motor learning by observing.

2-D-108 Frequency-specific activity in the subthalamic nucleus during isometric hand contraction

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Excessive beta oscillations (15-25Hz) in the subthalamic nucleus (STN) are associated with Parkinson's disease (PD) symptoms. Deep brain stimulation (DBS) of STN is thought to suppress these oscillations thereby improving symptoms. Physiologically, beta is also suppressed with motor tasks. The activity of

single-units and local field potentials (LFP) was measured during sustained isometric hand contractions during power and precision grips. The aim was to investigate different phases of movement, and how beta oscillations are modulated based on the number of muscles recruited and amount of force generated. PD patients undergoing implantation of DBS electrodes were asked to perform maximal voluntary contractions with a hand dynamometer during intra-operative microelectrode recordings. Spectral analyses of single cell and LFP activity determined peak frequency and power during the phases of each task. Firing rates of single units increased upon onset and offset of sustained contraction more profoundly during power grip. During contraction, cells tend to return to baseline firing. Beta oscillations are desynchronized upon onset and offset, but return during sustained contraction. Some patients develop hand tremor during contraction and consequently cells fire at the tremor frequency (5-8Hz). The power at the tremor frequency is greater during power grip. Frequency-specific activity appears to code information about muscle recruitment in STN differentially. Understanding STN mechanisms associated with motor control and PD symptoms can lead to improved treatment benefits of DBS.

2-D-109 Plasticity within early vestibular pathways: implications for the efficacy of a vestibular prosthesis

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Motor learning plays an essential role in fine-tuning the accuracy of complex movements as well as calibrating simple reflexes. The relative simplicity of vestibular pathways and their precise behavioral readout make it an excellent model system for studying mechanisms of motor learning. Here we examined the neural correlates of behavioral plasticity induced by applying temporally precise electrical stimulation to vestibular afferents in alert rhesus monkeys. Behavioral and individual vestibular nuclei neurons responses were recorded to link changes in neuronal activity across different sites within vestibular circuitry with changes in behavioral responses. Repeated stimulation markedly attenuated responses in neurons that receive direct vestibular nerve input. In contrast, single vestibular afferents showed no change in their responses to the same stimulation, suggesting that stimulation induced plasticity at the vestibular afferent to central neuron synapse. Interestingly, although stimulation caused a coincident decrease in evoked both eye and head movements, this attenuation was significantly less than that of the responses of neurons that mediate these reflex behaviors. Accordingly, we tested whether compensatory changes occurred in indirect inhibitory vestibular pathways. Surprisingly, responses of this neuron group showed no changes to comparable stimulation of the vestibular nerve. These findings suggest that rapid plasticity within indirect vestibular pathways compensates for the reduced efficacy at the first central synapse to ensure a robust behavioral output.

2-D-110 Effect of novel cannabinoid type 2 in an animal model of acute inflammatory orofacial pain.

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The aim of this study was to test the effectiveness of trans-caryophyllene (TC), a cannabinoid type 2 (CB2) agonist, in an animal model of acute inflammatory orofacial pain. Male Sprague-Dawley rats were used to evaluate the nociceptive sensorimotor responses evoked in the anterior digastric and masseter muscles by application to the tooth pulp of the inflammatory irritant mustard oil (MO). The left or right maxillary first molar pulp was exposed for the MO application. EMG activities in the mucles were

monitored continuously, first at baseline for 15 min, and then TC (20 mg/kg) or vehicle control (cremophor 0.05% plus saline) was administered intraperitoneally. After 30 min, MO (0.2 µl/95%) was applied to the exposed pulp. The MO application significantly increased EMG activities in the jaw muscles and the TC significantly reduced the MO induced increased EMG activities (two-way ANOVA followed by Bonferroni). These results suggest that TC can attenuate nociceptive sensorimotor reponses in this acute inflammatory orofacial pain model. The effectiveness of this novel CB2 compound in this pain model may have clinical potential for the development of novel pharmacological approaches for controlling acute inflammatory orofacial pain.

2-D-111 Adapted use of audiovisual information for person and object recognition in people with one eye

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The ability to identify people is essential for everyday social interactions. It can be quickly achieved based on identity information from cues such as a person's face and the sound of their voice. We asked how people with one eye, who have reduced visual input and altered auditory and audiovisual processing, will use face and voice information for person identity recognition. We investigated person (face and voice) and object (car and horn) identity recognition using an old/new paradigm. Participants were presented with pairs of faces and voices (Experiment 1), as well as, cars and horns (Experiment 2) and were asked to remember the identity pairings. Recognition of visual, auditory and audiovisual (congruent and incongruent pairings) identities in people with one eye were similar to binocular and monocular viewing controls. However, unlike controls, the addition of auditory information facilitated bimodal identity recognition for people with one eye but not controls. The addition of visual information facilitated bimodal object identity recognition but not bimodal person recognition for people with one eye while controls show the opposite pattern. Binocular viewing controls had better sensitivity for congruent compared to incongruent audiovisual pairings indicating that they based their person and object recognition according to their dominant modality (vision), whereas people with one eye did not. These results indicate that people with one eye may have adaptive strategies, such as not relying on vision as the dominant modality in order to perform similarly to controls.

2-D-112 Lack of adenylate cyclase 1 (AC1): Consequences on corticospinal tract development and on locomotor recovery after spinal cord injury

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Cyclic AMP (cAMP) signalling pathways are involved in axonal growth and regeneration. The calcium-calmodulin-stimulated adenylate cyclase1 (AC1),a regulator of cAMP levels,is strongly expressed in the corticospinal motorneurons (CSMN) in cerebral cortex layer V during development, but its role in the development of the corticospinal tract (CST) is unknown. In our study, we analyse the organization of the CST pathway using anterograde and retrograde tracers in the barrelless (brl) mouse that carries an inactivating mutation of the AC1 gene. We show that in brl mice the general organization of the CST is normal but there is an increase in the number of axons in the ipsilateral contingent in the dorsal and ventral medial funiculi of the cervical spinal cord. The density of CSMN in layer V of the motor cortex is increased in brl compared to wild-type mice. Thus,lack of AC1 likely perturbs late phases of CSMN and CST development. Moreover, our study analyses the motor recovery after a spinal cord injury (SCI). We

find that brl mice show enhanced locomotor functions as assessed by the BMS (Basso mouse scale) as early as 6h and up to 6 weeks after SCI, indicating a smaller responsiveness of brl mice to SCI. It is therefore possible that developmental effects on motor systems might decrease the locomotor effects consecutive to a SCI. This point is particularly important with regards to the use of transgenic animals for testing SCI recovery.

2-D-113 Cholinergic denervation of the rat posterior parietal cortex impairs complex stimulus discrimination

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Cortical cholinergic activity has been shown to influence attentional and visual processes. The role of basal forebrain cholinergic innervation and neuromodulation of the cortex is often studied in visual attention tasks without consideration of its regional specificity. Here, the study was aimed at differentiating the role of cholinergic neuromodulation on specific cortical areas during visual attention tasks. Rats were tested in motion direction discrimination tasks with or without local lesions of the cholinergic fibers. Two levels of difficulty were tested: discrimination of a simple or a complex stimulus, the latter being processed in high cognitive cortical areas. 192 IgG-Saporin intraventricular or intracerebral injections were performed to specifically lesion the cholinergic fibres in either the entire cortex, the medial prefrontal cortex, the posterior parietal cortex or the primary visual cortex. Performance in the motion discrimination of the simple stimulus was decreased only for rats with lesion of the entire cortical cholinergic innervation. Performance in the motion discrimination of the complex stimulus was decreased for rats with cholinergic lesion of the entire cortex or posterior parietal cortex only. Thus, our results show that the cholinergic modulation of the different cortical areas is involved in different visual functions. Moreover, the cholinergic neuromodulation of the posterior parietal cortex seems critical for complex stimulus discrimination.

2-D-114 Effects of Passive Stretch on Reflex Excitability in Neurologically Intact Participants

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Neurotrauma can result in spasticity which impairs motor control and walking ability. Spasticity is characterized by hyperactive stretch and electrically evoked Hoffmann (H-) reflexes. Therapeutic stretching is used in spasticity management, but long-term physiotherapy services are expensive and inaccessible to many Canadians. Commercial devices that provide stretch without a therapist have recently been developed and may be useful, however quantified effects on reflex excitability are unknown. This study examined the effects of 30 minutes of passive stretching on H-reflex excitability and range of motion (RoM) at the ankle joint in neurologically intact participants. H-reflexes were evoked in the soleus muscle by stimulation of the tibial nerve, and along with RoM, were recorded from 9 participants before and after device application. Maximal H-reflexes (40.0±19.58%, 36.2±20.6%; all as % maximum direct motor response (Mmax)), those at 50% of maximal current (23.9±12.38%, 24.4±13.93%), and threshold current (49.1±12.6%, 52.7±9.9%) did not statistically differ pre- to post-stretching. Furthermore, ankle joint RoM pre- to post-stretching did not significantly increase (decrease of 3.6±16.64%). These data suggest that 30 min of passive stretching at the ankle failed to influence spinal cord reflex excitability.

E – Homeostatic and Neuroendocrine Systems

2-E-115 Subfornical organ neurons respond differentially to applications of cholecystokinin and angiotensin II

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The subfornical organ (SFO) is one of three sensory circumventricular organs, a family of brain regions distinguished by their increased vasculature and lack of a blood brain barrier. Previous research has demonstrated its role in monitoring circulating hormones such as angiotensin II (ANG) and cholecystokinin (CCK), which induce drinking and a decrease in eating behaviour, respectively. Given that the SFO is comprised of a diverse group of neurons, differing in both projection site and anatomy, we sought to discover whether the same SFO neurons sense both ANG and CCK or if they exclusively sense one hormone but not the other. Using male Sprague Dawley rats, aged from 21-42 days, we measured intracellular calcium ([Ca2]¡) in dissociated SFO neurons. It was observed that 67.4% (n=86) of neurons responded to 100nM ANG (mean change in [Ca2]¡ ,105.7 ± 14.8 ratiometric units) and 41.7% (n=108) responded to 100nM CCK ([Ca2]¡, 82.17 ± 14.55 ru). When both hormones were applied in randomized order, 27.9% (n=86) responded to ANG and CCK, 38.4% responded exclusively to ANG, 15.7% responded exclusively to CCK, and 26.7% responded to neither signal. Using perforated current-clamp electrophysiological recordings and applying 10nM of the aforementioned hormones, it was observed that 17.6% (n=17) of SFO neurons responded to ANG and CCK, 41.2% responded exclusively to ANG, 0% responded exclusively to CCK, and 41.2% responded to neither. These findings suggest SFO neurons are not a homogenous population but likely differ in role and function, perhaps based on their projection site.

2-E-116 Inhibition of corticotropin-releasing factor (CRF) by teneurin C-terminal associated peptide (TCAP)-1: A molecular switch to regulate mitochondrial function.

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Although well established in its role to regulate the hypothalamic-pituitary-adrenal (HPA) axis, CRF plays a number of neurological and HPA-independent roles with respect to the regulation of the organismal stress response. CRF, by itself, can increase anxiogenic responses in a number of behavioural models including elevated plus maze, open field, acoustic startle, and cocaine-reinstatement. We have shown that in each case, the anxiogenic aspects of CRF can be blocked by treatment with teneurin C-terminal associated peptide (TCAP)-1. TCAP-1, an evolutionarily ancient neuropeptide that regulates cellular energy production, and intracellular calcium concentrations ([Ca2+]i), and is generally neuroprotective in vitro. However, the mechanism by which this occurs is not clear. To better understand the physiological role of TCAP-1 it is necessary to further characterize this signalling system. The aim of this study was to investigate TCAP-1 activated signalling pathways by assessing the effect of TCAP-1 treatment on [Ca2+]i. Using immortalized hypothalamic neurons and live-cell fluorescent imaging we have determined that TCAP-1 decreases [Ca2+]i, and at the same time depolarizes mitochondrial membrane potential, indicating uptake of intracellular Ca2+ into mitochondria. Furthermore, we show that TCAP-1 treatment prevents the CRF-induced increase in [Ca2+]i suggesting a role for TCAP-1 in mitigating the CRF-induced stress response. Thus, taken together these findings indicate that TCAP-1 may suppress the actions of CRF by regulating cytosolic calcium and mitochondrial activity.

2-E-117 Prostaglandin E2 drives neuroendocrine stress response through presynaptic inhibition of GABA release

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Immune-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis and ensuing release of anti-inflammatory glucocorticoids are critical for the fine tuning of the inflammatory response. Although prostaglandin E2 (PGE2) has a well defined role in the immune-induced activation of parvocellular neuroendocrine cells (PNCs) in the hypothalamic paraventricular nucleus (PVN), it remains unclear if and how PGE2 modulates synaptic inputs onto PNCs. Using whole-cell patch clamp recordings obtained from PNCs in an ex vivo hypothalamic slice from Sprague-Dawley rats, we evaluated the effect of PGE2 on GABA-mediated inhibitory synaptic transmission. Bath application of PGE2 (0.01−100 μM) dose dependently decreased the amplitude of evoked inhibitory postsynaptic currents (eIPSCs) with maximal effect at 10 μM. The PGE2-mediated depression of eIPSCs had a rapid onset (significant inhibition by 3 min), was long-lasting (>25 min after wash out) and accompanied by an increase in paired pulse ratio. In addition, PGE2 decreased the frequency but not the amplitude of spontaneous IPSCs, suggesting that PGE2 acted at a presynaptic locus to decrease the probability of GABA release. The effects of PGE2 was mimicked by a selective agonist for EP3 (salprostone) and, conversely was blocked by an EP3 antagonist (L798,106). We demonstrate that PGE2-EP3 signaling causes a long-lasting depression of GABA release onto PNCs, providing a plausible mechanism for the disinhibition of HPA output during inflammation.

2-E-118 Effects of Intranasal Insulin Administration on Memory in the 5XFAD Mouse Model of Alzheimer's Disease

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Alzheimer's Disease (AD) is a cognitive neurodegenerative and metabolic disorder. Decreased glucose utilization due to insulin resistance and insulin deficiency occurs in AD patients. Insulin modulates memory processing, and insulin administration to the CNS through intranasal delivery (IND) improves performance on memory tasks in mice. We investigated the effects of 11 days of insulin IND (0, 0.87 or 1.75 U/day) on memory performance, overall health, PKB (akt), and insulin receptor levels in the 5xFAD mouse model of AD and their wild-type (WT) littermates at 5-6 months of age. Memory was assessed before and during treatment using T maze spontaneous alternation, novel object recognition, and trace and contextual fear conditioning tasks. Weight, peripheral blood glucose and frailty were measured to examine the health of the mice pre- and post- treatment. Western blots were used to measure levels of akt and insulin receptor. Insulin IND treatment had no effects on memory performance, body weight, frailty or plasma glucose levels in 5XFAD or wild-type mice. At all doses, the 5xFAD mice weighed less than wild-type mice ($p<0.05$). Irrespective of dose, insulin receptor α levels were higher in 5xFAD mice and insulin receptor β levels were higher in WT mice, however the level of insulin receptor β increased in 5xFAD mice with insulin dose ($p<0.05$). Phosphorylated akt (p-akt) was higher in WT mice compared to 5xFAD mice ($p<0.05$) and as insulin dose increased, p-akt levels increased in both genotypes. IND insulin did not affect behavior in our mice, but had effects in the brain.

2-E-119 High fat diet primes excitatory synapses of orexin neurons to express long term depression

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Orexin neurons protect against weight gain. Therefore high-fat diets may cause weight gain by reducing orexin activity. Since orexin neurons are regulated by excitatory input, we tested the hypothesis that high fat diet (HF) suppresses excitatory transmission to these neurons. To test this, male rats were fed a HF or low-fat (LF) diet for one week and then patch clamp recording was performed to record evoked excitatory postsynaptic currents (eEPSC) in orexin neurons using brain slices. When high frequency stimulation was applied to presynaptic fibers, we found no effect on eEPSC amplitude in LF orexin neurons, while HF neurons expressed long-term depression (LTD). As the LTD was accompanied by an increase in paired pulse ratio, it likely has a presynaptic locus. We also found that this LTD is independent of NMDARs but requires group 1 mGluR signaling. Using a low-affinity competitive AMPAR antagonist, we found that stimulation-induced synaptic glutamate concentrations were higher under HF, which may explain activation of mGluRs. Indeed, increasing synaptic glutamate by blocking glutamate uptake was sufficient to induce LTD in the LF condition. Involvement of a retrograde transmitter is currently under investigation. To conclude, HF exposure leads to the expression of activity-dependent presynaptic LTD of evoked EPSCs in orexin neurons. This is mediated by group 1 mGluRs, which may be activated by increased synaptic glutamate. These data show that high-fat diets can inhibit orexin activity through modulation of excitatory inputs.

2-E-120 Adropin Elicits Concentration-Dependent Effects on Hypothalamic Paraventricular Nucleus Neurons

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Adropin, a peptide hormone encoded by the Energy Homeostasis Associated (Enho) gene, has been observed to have metabolic roles in the periphery but unknown actions within the brain. The hypothalamic paraventricular nucleus (PVN) is an important autonomic control center required for regulating energy balance, and is therefore a potential target for centrally acting adropin. In the present study, we used whole-cell current-clamp techniques to examine the effects of adropin on the excitability of neurons within the PVN of the rat. All three neuronal subpopulations (magnocellular neurosecretory, parvocellular preautonomic, and parvocellular neuroendocrine) in the PVN were found to be responsive to bath application of 10 nM adropin, which elicited responses in 72% of cells (n=54), with 59% depolarizing (mean: 4.9 ± 2.3 mV) and 13% hyperpolarizing (mean: -5.0 ± 2.8 mV). Concentration-dependent (100 pM-100 nM) depolarizations were observed in all three types of neurons (mean depolarizations: 100 pM, 3.8 ± 0.9 mV, n=12; 10 nM, 4.9 ± 2.3 mV, n=32; 100 nM, 7.0 ± 2.0 mV, n=4), while no neurons tested (n=6) responded to 1 pM adropin (mean: 1.1 ± 0.4 mV). The depolarizing effects of 10 nM adropin were maintained in the presence of tetrodotoxin in 86% of neurons tested (mean: 4.0 ± 2.3 mV, n=7). These results suggest that central adropin may exert its physiological effects through direct actions on neurons in the PVN.

F – Cognition and Behavior

2-F-121 Determining cognitive deficits in mouse models of Alzheimer's disease using touchscreen tasks: improving the transition from bench to bedside

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Classical behavioural tasks used to test cognition in mouse models are in general non translatable to humans and usually low throughput due to a lack of automation and reproducibility. The Bussey-Saksida touchscreen tasks provide a new paradigm for testing cognitive deficits in animal models and addresses most of the pitfalls above. In this study, using the 5-Choice Serial Reaction Time Task (5-CSRTT), which assesses attention and related cognitive domains, we compared longitudinally (4, 7 and 10 months of age), the performance of males and females of two different mouse models Alzheimer's Disease (AD) (5XFAD and 3xTG-AD) We tested reproducibility of the tests by performing similar experiments at the University of Western Ontario and University of Guelph and used the data to generate an online database of mouse performance in cognitive tests. In both sites we observed similar attention performance in the two AD mouse lines when probed in the 5-CSRTT. Both 5XFAD males and females showed attention deficits at 7 months of age and male and female 3xTG-AD mice showed deficits in attention earlier at 4.5 months of age. This work provides an initial screening of comparative cognitive deficits in distinct mouse models of AD showing reproducibility and robustness of results. These automated tasks lend themselves to high-throughput, and during this project we have been able to test close to 300 mice per day. These results point to the potential usefulness of the touchscreens behavioural tests as a powerful tool for drug screening in AD and other neurodegenerative diseases.

2-F-122 Longitudinal assessment of behavioural flexibility and visual spatial integration learning in the 5xFAD mouse model of Alzheimer's disease using automated touchscreen systems

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A recent advancement in the testing of mouse models of neurological disease has been the use of automated touchscreen equipped operant chambers to assess cognition with sophisticated behavioural tasks. We have used this approach to characterize the 5xFAD transgenic mouse model of Alzheimer's disease, which expresses several mutations on the amyloid precursor protein and presenilin-1 genes to model severe amyloid pathology. Male and female 5xFAD mice were tested on the pairwise discrimination (PD) and the paired associate learning (PAL) task. The PD task is designed to assess visual discrimination learning and behavioural flexibility, while the PAL task is designed to assess visual spatial learning. 5xFAD mice were tested at 4 months, 7 months, and 10 months of age for PD, and were tested on PAL at 4 months and 10 months. Results from the PD task demonstrated that neither female nor male 5xFAD mice had deficits in visual discrimination or behavioural flexibility. Results from the PAL task indicated no difference in the rate of acquisition; however, overall acquisition levels were lower than previously reported for other strains. Following a 2 week retention delay, 5xFAD mice were found to have deficits in long-term retention of the PAL task. These results, in conjunction with findings from other transgenic strains, will become part of a large scale database that will further aid AD research. The touchscreen operant chamber approach to behavioural testing should help to aid the process of AD therapeutic development because of its controlled and high-throughput nature.

2-F-123 Longitudinal assessment of behavioural flexibility and visual spatial integration learning in the 3xTG mouse model of Alzheimer's disease (AD) using automated touchscreen systems

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A recent advancement in the testing of mouse models of neurological disease has been the use of automated touchscreen-equipped operant chambers to study cognition with sophisticated behavioural tasks. Here, we assessed several cognitive domains in 3xTG mice, a transgenic model of familial AD, expressing mutant transgenes on the amyloid precursor protein (APP) and PSEN1 genes, driving Aβ42 overproduction and accumulation of amyloid-β-plaques, and mutant tau, triggering accumulation of neurofibrillary tangles. Male and female 3xTG mice were tested on the pairwise discrimination (PD) task at 4, 7 & 10 months of age, and paired associate learning (PAL) task at 4 & 10 months. PD is designed to assess visual discrimination learning and behavioural flexibility, while PAL can assess visual spatial learning. Female and male 3xTG mice had minimal deficits and overall intact visual discrimination and behavioural flexibility in PD. Transient PD accuracy deficits were observed in females. In PAL, early cognitive deficits were observed in 3xTG males at 4 months, but not evident at 10. In general, all mice (wildtype, transgenic, male and female) demonstrated poorer performance at 10 months suggesting aging-related cognitive decline. These results, in conjunction with our findings from other transgenic strains, will become part of a large scale database to further aid researchers studying AD. The automated touchscreen operant chamber approach to behavioural testing should help to speed the process of AD therapeutic development because of its greatly controlled and high-throughput nature.

2-F-124 Functional Mapping of Brain Circuits Supporting Social Modulation of Pain in Mice

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Although empathy had been traditionally considered to be a higher level affect/cognitive process expressed exclusively by humans, recent developments have placed this anthropocentric view into question. It is now accepted that many species, including rodents, can engage in empathetic behavior. Recent studies have demonstrated that mice have the ability to transmit pain status between paired cage-mates resulting in contagious pain hypersensitivity (hyperalgesia). Interestingly, this transmission of pain status only occurred during interactions where both mice of the dyad are in pain and shared a social history with each other; unfamiliar mouse dyads produced the opposite response inducing marked analgesia. Because the detection of discomfort, distress or pain in other members of the same species carries information of high survival value, extensive efforts have been directed at elucidating the neurobiological substrates that underlie emotional contagion. To address this, we performed whole-brain mapping by examining expression of the IEG c-fos, a marker of neuronal activation, in stranger or familiar mice dyads, as well as isolated mice following treatment with dilute acetic acid. We found greater Fos+ neurons in the basolateral amygdala of familiar mice compared to isolated or unfamiliar mice consistent with the role of this structure in appraisal of threat vs. safe cues. We are currently examining neuronal activation of multiple cortical and limbic brain regions. These findings provide a starting point for mapping the neural circuitry that support emotional contagion.

2-F-125 Glutamatergic SubC cells are the core of the REM sleep network

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It remains unclear which neuronal circuit and neurotransmitter mechanism triggers REM sleep. Glutamatergic neurons in the subcoeruleus (SubC) are active during REM sleep and are anatomically well positioned to control the muscle atonia and cortical activity that defines REM sleep, but it is unknown if these neurons actually influence or generate REM sleep. Here, we aimed to determine how optogenetic manipulation of glutamatergic SubC neurons impact REM sleep. To control the neuronal activity of the glutamatergic SubC neurons, we bilaterally infused 200nL of AAVs containing either a light-sensitive excitatory opsin or a light-sensitive inhibitory opsin or an inert control protein into the SubC of 27 Vglut2-cre mice. Animals were instrumented for EEG and EMG recordings. Neurons were light-manipulated either independently of behavioral state or specifically during REM sleep. We found that activation of SubC neurons significantly increased the probability of entrance into REM sleep and prolonged the duration of REM sleep episodes ($p<0.01$). Continuous inhibition throughout all behavioral states led to a decrease in REM sleep amounts ($p<0.01$) by abruptly shortening the duration of REM sleep episodes ($p<0.01$). Excitation of SubC neurons led to a stabilization of REM sleep muscle atonia, whereas inhibition led to a significant increase in motor activity above NREM sleep level ($p<0.01$). These results support the hypothesis that glutamatergic SubC neurons are at the core of the circuit which generate REM sleep and its characteristics.

2-F-126 The Hypnotized Brain: An Examination of the iEEG Correlates of Neutral Hypnosis

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This research investigates the neurophysiological mechanisms of hypnosis using intracranial electroencephalography. This methodology removes resolution problems associated with functional imaging. Patients with intractable epilepsy, and implanted as part of their diagnostic exam, were hypnotized. Neutral hypnosis was measured following a standard induction procedure, and before the administration of hypnotic suggestions. Patients with high and low hypnotizability were tested and compared. Phase based synchronization for connectivity analysis was calculated for three different conditions: prehypnotic state (eyes open and closed), neutral hypnosis (eyes closed) and posthypnotic state (eyes open and closed), across multiple frequency bands. The intersite phase clustering difference between all the intracranial electrodes across delta, theta, alpha, beta and gamma frequencies, was computed for all conditions. In high hypnotizable patients with bi-temporal burr holes, we found more intersite synchronization, for theta and alpha bands, in the hypnotic condition than in the eyes closed conditions, and a more modular organization (more partitionable) in both the hypnotic and the eyes closed conditions, compared to the eyes open conditions. Phase synchronization distribution distance for all bands between hypnotic and posthypnotic states was shorter in high than in low hypnotizable patients. Our results suggest that hypnosis represents a genuine brain state whose distinctiveness from states of deep relaxation is in need of clarification.

2-F-127 Modelling gambling disorder in rats: interaction of responding for uncertainty and reward predictability on dopamine sensitization and risky decision-making

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Gambling Disorder (GD) is a behavioural addiction that leads to individual and social harm. In GD, the mesolimbic dopamine (DA) system may be hyperactive or "sensitized". However, it is unclear whether

the sensitization results from gambling exposure, which includes exposure to uncertain reinforcement. To address this issue, male Sprague-Dawley rats (N=40) were trained twice daily on a fixed or variable ratio (FR/VR) schedule of nosepoking to obtain a conditional light stimulus (CS) that predicted reinforcement (sacharrin) 50% or 100% of the time. The VR50% condition was the most uncertain, whereas the FR100% condition was the least. After 66 sessions, sensitization was inferred as an enhanced locomotor response to amphetamine; the VR groups (VR50%, VR100%) showed a higher response vs. the FR groups (FR50%, FR100%). As increased risky decision-making is observed in subjects with GD, decision-making was assessed using the rat gambling task. During 40 x 30min daily session, rats chose between advantageous and disadvantageous options. Although disadvantageous options yield larger immediate gains (sucrose pellets), they are also associated with greater long-term loss (timeout periods) and are therefore disadvantageous in the long-term. The VR50% group made less advantageous choices than the FR100% group. In sum, an uncertain schedule of reinforcement induces sensitization of DA. Also, the unique addition of an unpredictable cue resulted in risky decision-making. Therefore distinct aspects of gambling-like scenarios may differentially modulate sensitization and decision-making.

2-F-128 Resting-state functional connectivity studies in common marmoset monkeys at 9.4T

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Interest in the common marmoset (Callithrix jacchus) is growing rapidly as it is poised to become the leading candidate transgenic primate model. In contrast to the established Old World macaque, little is known about the functional organization of the saccade circuitry in these New World primates. Here we used resting-state fMRI from 12 macaques and 4 marmosets, to examine the functional connectivity of the superior colliculus (SC), a major node in the neural network underlying saccade control. Macaque data and marmoset data were obtained using custom-built transmit/receive coils on a 7T and 9.4T MR scanner, respectively. In both species, a seed region analysis revealed functional connectivity of a frontoparietal network with the SC. In macaques, the network overlapped with previously described frontal eye fields connectivity patterns which included the intraparietal sulcus, dorsolateral prefrontal cortex, anterior cingulate cortex, and supplementary eye fields. Visualization of marmosets' cortical functional connectivity on a surface-based registration revealed the strongest connectivity in frontal cortex in areas 6DC, 6DR, 8AC and in parietal areas PFG and PF. In addition, independent component analysis successfully extracted 9 resting state networks in marmosets, greatly overlapping with corresponding networks in macaques. The frontoparietal network was among those identified, overlapping with the SC-connectivity maps. The results support an evolutionarily preserved frontoparietal system and provide a starting point for invasive neurophysiological studies in marmosets.

2-F-129 Somatosensory attention identifies both overt and covert awareness in disorders of consciousness

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Patients with disorders of consciousness, who are behaviourally non-responsive due to severe brain injury, present a diagnostic challenge to physicians. Neuroimaging techniques have been developed to assess awareness independent of a patient's ability to speak or move. Unfortunately, the evidence for the sensory and cognitive abilities of these patients across and within diagnostic categories is

inconsistent, despite substantial clinical and scientific interest. We evaluated a sample of eleven patients with disorders of consciousness using a vibrotactile attention task and assessed their brain responses with electroencephalography. We also assessed the patients with a neuroimaging-based assessment of covert command following and a standardised clinical assessment. Only patients who could follow commands demonstrated evidence of attentional orienting. A simple somatosensory oddball procedure can characterise the level of neurocognitive preservation in patients with disorders of consciousness. This paradigm provides a valuable addition to neuroimaging approaches intended to improve diagnostic accuracy for these disorders and converging evidence for the utility of such techniques in general.

2-F-130 Social isolation reveals a dopamine-independent rewarding motivational response to acute nicotine that is not observed in group-housed mice

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Drug abuse, specifically nicotine addiction, is a worldwide epidemic that has led to many deaths. Recent research has suggested that social factors play an important role in both the initial response to abused drugs and the transition to addiction. In order to investigate such factors, we used a place conditioning paradigm to examine the effect of single- versus group-housing on the acute conditioned response to nicotine in nondependent C57Bl/6J mice and compared these nicotinic motivational effects with those elicited after dopamine receptor antagonism. Mice that were single-housed (and therefore socially isolated) for two weeks prior to conditioning and pretreated with the dopamine receptor antagonist α-flupenthixol prior to acute nicotine found nicotine rewarding. However, mice that were group housed or were single-housed only during conditioning did not show this conditioned rewarding response. These results suggest that the stressful experience of social isolation makes single-housed nondependent mice behave as if they are nicotine-dependent and shifts the balance of acute nicotine's aversive and rewarding effects, such that socially isolated mice are more likely to experience the acute rewarding effects of nicotine after blockade of dopaminergic receptors. These results further highlight the important role that social factors play in the motivational response to acute nicotine

2-F-131 Place coding in the monkey hippocampus is task-dependent during virtual navigation

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The hippocampus has long been studied as a component of two functional systems in the brain: first, integrating contextual information for episodic memory; and second, supporting spatial navigation. Though much is known about hippocampal networks supporting spatial mapping in rodents, whether/how this activity is conserved in humans and non-human primates is debated. Furthermore, experimental constraints limit the study of contextual learning in rodents, leaving a gap in our understanding of how the hippocampus dynamically supports both functions. To study hippocampal activity during navigation and learning, we recorded single-neuron spikes from the hippocampus of two rhesus monkeys (Macaca mulatta). Each monkey completed two tasks in a common virtual reality (VR) environment: 1) randomly foraging for rewards, or 2) a context-object associative learning task. Of all single units active in both tasks (n=223), 44.8% showed place-selective firing during foraging, while 63.2% were place-selective during contextual learning in the same VR environment. Concordantly, decoding accuracy for spatial position in the VR maze using all recorded neurons is higher during

contextual learning than foraging. Prediction accuracy is further improved in this task when decoding task-relevant behaviour of the monkeys, rather than spatial position per se. These cross-task analyses suggest that previously stereotyped hippocampal activity patterns vary dynamically according to behavioural demands of the task are engaged in.

2-F-132 Characterization of a rostrocaudal differentiation in the nucleus accumbens core in processing conditioned cues of conflicting valence

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The nucleus accumbens is a site of integration of positively and negatively valenced information and action selection. Here we characterized a rostrocaudal differentiation within the core subregion in the mediation of approach or avoidance in response to conditioned cues in a conflict situation. Rats were trained to associate visuo-tactile cues with appetitive sucrose, aversive foot-shocks and neutral outcomes. In a test of motivational bias, the aversive and appetitive cues were superimposed in a maze arm and rats' exploratory bias was measured for this arm vs. a neutral cued arm. Animals receiving GABA receptor agonists in the caudal core region displayed a bias in the direction of aversion, whereas inactivation of a central site resulted in a lesser bias toward aversion, and disruption of activity in the rostral core elicited an ambivalence similar to controls. Additionally, separate tests were conducted which measured exploratory preference for the arms containing the appetitive versus neutral cues, and the aversive versus neutral cues. Animals receiving GABA receptor agonists in the caudal core region spent a decreased proportion of time in the aversive arm as compared with control animals, as well as a decreased proportion of time in the appetitive arm as compared with controls. The results delineate a rostrocaudal differentiation in valence processing in the accumbens core in situations of conflict, and suggest that the behaviour observed after inactivation likely results from a composite of effects on the processing of both appetitive and aversive information.

2-F-133 A comparison of fMRI-based functional connectivity during resting state and naturalistic stimulation

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A common method to examine brain-wide functional connectivity is to investigate BOLD fluctuations when the brain is at rest. A more recent method assesses connectivity as participants attend to rich naturalistic stimulation, such as movies. Although the same brain networks have been observed in both cases, little is known about differences in connectivity strength within and between these networks in the two conditions. Here, we compared functional connectivity during movie watching and resting state in well-established brain networks of healthy participants (N=13). We found no significant difference in within-network connectivity between movie watching and resting state. By contrast, between-network connectivity was significantly higher across the brain in the resting state. The pattern of within-network connectivity revealed both functional groupings and dissociations during movie watching that were absent in the resting state. In particular, the dorsal attention, control, salience and sensorimotor networks were strongly connected with one another, and weakly correlated with the default-mode, visual and auditory networks. Further, these last three did not pair with any other networks. These results suggested that the brain re-organizes itself in a highly specific manner when exposed to naturalistic stimuli, akin to real-life events, as compared to when it is at rest. Therefore naturalistic

stimulation offers a highly sensitive method to study the brain's functional response to information processing and how it goes awry in different patient populations.

2-F-134 Effects of socially-based ensemble music training on children's executive functions: ERP evidence

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Objectives: We examined the effect of participation in OrKidstra, an ensemble social music program run by The Leading Note Foundation, on children's ability to attend selectively, evaluate and exert cognitive control in an auditory Go/No-Go task, as reflected by children's Event-Related Potentials (ERPs). Methods: Sixteen children (eight in OrKidstra and eight in a comparison group; four males per group; ages 9-12 years) from low family socioeconomic status (SES) completed a pediatric hearing test followed by a standard version of the auditory Go/No-Go task using pure tones at 1100 and 2000Hz. Accuracy, reaction times, and concurrent high-density tone-locked ERPs were measured. Results: Accuracy, errors, and reaction times for the Go/No-Go task were not significantly different between groups. However, children in the OrKidstra group had significantly higher auditory discrimination for tones at 500, 1000, and 2000Hz. ERP analysis showed that compared to the other group, the OrKidstra group generally had earlier but smaller N200 and P300 peaks, and larger prefrontal late positive potentials (P600-950), which are waveforms associated with auditory perception, stimulus evaluation, and response control, respectively. Conclusions: The data suggest that, relative to the comparison children, the OrKidstra children show faster and more efficient neural processing (unconfounded by motor response) associated with perception, evaluation, and inhibition to auditory stimuli. This study highlights the importance for socially-based musical intervention programs targeting low SES children.

2-F-135 The role of noradrenaline in the affective properties of metabolic stressors in laboratory rats

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The role of noradrenaline in the affective properties of metabolic stressors in laboratory rats Thomas Horman and Francesco Leri Introduction: There is some evidence that hypoglycemia induces depressive-like behaviours in laboratory animals and alters mood state in humans. Therefore, it is conceivable that glycemic stressors may be useful to explore the homeostatic dimension of negative affect and its sensitivity to different antidepressant drugs. The current study tested the hypothesis that noradrenaline (NE) is involved in the negative affective response induced by hypoglycemia. Methods: Thirty-six male Sprague-Dawley rats were injected with the glucose antimetabolite 2-deoxy-D-glucose (2DG; 0, 300 or 500 mg/kg) and tested for the development of conditioned place avoidance (CPA). 2DG was paired with an initially preferred environment during an 8 day conditioning period and avoidance behaviour was determined by comparing the time spent in this environment before and after conditioning. In a separate group of animals, clonidine (0, 10 or 40 ug/kg), a noradrenergic alpha2 receptor agonist, was administered concurrently with 500 mg/kg 2DG. Results: Systemic 2DG produced a dose-dependent CPA which was significantly reduced by coadministration of clonidine. Conclusions: These results suggest that hypoglycemia induces a negative affective state that is dependent on acute NE hyperactivity. Understanding neuropharmacological links between mood and homeostatic stressors is likely to reveal useful biomarkers to improve the diagnosis and treatment of depression.

2-F-136 The effects of fornix stimulation on memory in non-human primates.

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Deep brain stimulation to the fornix (DBS-f) is under clinical-trial evaluation in the treatment of memory decline in Alzheimer's disease (AD). Whereas results have been inconsistent in these early clinical studies1, 2, 3, stimulation of hippocampal-targeting tracts in rodents has been shown to alter hippocampal function and memory4, 5. One key difference is that the rodent studies commonly restrict stimulation to fixed time windows after encoding, during putative memory consolidation windows. Objective: To determine whether use of time-blocked DBS fornix (DBS-f) stimulation following encoding will alter performance on an episodic-like memory task in macaques. An adult female macaque underwent surgical implantation of two DBS electrodes targeting each hemisphere's post-commissural fornix. This configuration (100 µs biphasic pulses at 100-Hz) emulates the stimulation conditions used in AD clinical trials. In addition, we implanted multiple recording tetrodes in the left hippocampus. 4-day testing sets consisted of 30 trial-unique 'target' objects in scenes to be learned, followed by the stimulation condition (1 hour @100-Hz or OFF). Memory for target objects in scenes was indicated by gaze fixation on the (un-cued) target object, tested at a 1-day lag, and again at 48 or 72-hour lags. Preliminary results suggest that memory is relatively unaffected by stimulation when tested 24 hours post-acquisition, but consecutive days of 100-Hz stimulation yield modest memory improvements. Initial findings warrant further study of the timing and long-term effects of DBS-f on memory.

2-F-137 Behavioural characterization of Grk3 knockout mice

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G protein-coupled receptor kinase 3 (Grk3) belongs to the G-protein coupled receptor (GPCR) kinase family, which phosphorylate ligand-activated GPCRs, leading to beta-arrestin binding and termination of signaling. Grk3 is expressed in the brain, notably in cortex, ventral striatum, and hippocampus. Association studies have identified Grk3 as a susceptibility gene for bipolar disorder. Decreased expression of Grk3 has been detected in post-mortem samples from bipolar disorder patients and from patients with schizophrenia. We asked whether Grk3 null-mice would make a good translational model and investigated their behavioural phenotypes. Compared to C57Bl6/J controls, Grk3-/- mice have disruption of prepulse inhibition and show more sensitivity to amphetamine in a locomotion test. In terms of cognition, we find no differences in working or long-term memory based on Y-maze, T-maze and Morris Water Maze tests. Although the two groups performed similarly in the light-dark box, and elevated-plus maze, we observed increased tone-paired freezing in a fear conditioning paradigm and increased corner time combined with decreased peripheral rearing (explorative behaviour) in the open-field. These data are suggestive of a mild anxiety phenotype although more studies are required to pinpoint the exact manifestation of this anxiety. In summary, we have detected behavioural changes in Grk3-null mice consistent with rodent models of psychosis-like behaviour indicating these mice would be useful in the study of the psychosis aspect found in both schizophrenia and bipolar disorder.

2-F-138 Implicit Learning Facilitates Cognitive Control in a Response Switching Task

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Previous research demonstrated increased frontal theta oscillatory power in a go/switch task over a go/no-go task (Isabella et al., 2015). We hypothesize that this was due to differences in cognitive control. The primary objective of this study was to determine whether implicit learning improves performance on a cognitive control task, with the long-term goal of identifying cortical oscillations underlying differences in cognitive control. Subjects performed 7 blocks of a go/switch task, where stimuli '1', '2' and '4' required a right index finger button press (Go), but stimulus '3' required a left index finger press (Switch). Unbeknownst to the subjects, the stimuli were presented in a repeating 8-trial pattern (3-1-4-3-2-4-1-2), known to induce implicit learning in a serial reaction time task (Gabriel et al., 2011). 90% of trials presented the stimulus with the pattern intact (P), whereas 10% of trials presented the stimulus not according to pattern (nP). Reaction times (RT) for nP-Switches ('3' stimulus out of pattern) were longer than P Switches ('3' stimulus within pattern; $p < 0.02$). Additionally, RT for nP-Go's in place of Switches (i.e. the pattern stimulus called for '3') were longer than P-Go's ($p < 0.001$). Longer RT following nP-stimuli over P-stimuli when switches are involved demonstrate that subjects learned to anticipate Switch trials and subsequently improved their performance on the cognitive control task. Future studies will test differences in brain activity accompanying increased cognitive demands using this task.

2-F-139 Molecular pathways responsible for NMDA receptor-mediated behavioural plasticity.

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Critical periods of neurodevelopment are stages of pre- or postnatal development where transient impairments in neurotransmission have lasting effects on the integrity of that neural system. We asked whether the neural circuitry that mediates fear learning and memory was vulnerable to pre- and postnatal impairments in NMDA receptor transmission. To ask this question, we used mice that have a developmental reduction in NMDA receptors that can be rescued in adult mice. With this model we can also study the gene expression patterns that occur during fear learning, and whether these patterns are also normalized when NMDA receptor expression is rescued. Three groups of mice were studied: wildtype mice, NR1 knockdown mice, and NR1 rescue mice (having adult rescue of NMDA receptor levels). NR1 rescue mice showed improvements in behaviours related to executive function and anxiety (see Mielnik et al. poster). We studied gene expression in the hippocampus of learning associated genes (ARC, CAMKIIα, FOS, NR4A1, EGR1, DUSP1, HOMER1A and BDNF) and found that NR1 knockdown mice had reduced basal gene expression of BDNF and NR4A1. Studies are underway to determine whether NR1 rescue mice have behavioural improvements in fear memory, and whether the induction of learning associated genes is restored. Our research will determine whether there are lasting effects of developmentally impaired glutamate signaling on cognitive function.

2-F-140 Wnt inhibitor, IWP-2, impairs expression of amphetamine-produced conditioned place preference in rats

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Dopaminergic neurotransmission is thought to drive reward-related incentive learning and the development of addictive behaviour. Amphetamine (AMPH) elevates extracellular dopamine (DA), which prolongs DA receptor signalling in the striatum and has been shown to elicit incentive learning, wherein neutral stimuli when paired with AMPH gain the ability to produce approach responses. It has previously

been shown that Wnt signalling is increased in the rat nucleus accumbens (NAc) after the injection of AMPH compared with saline. The present study aimed to assess the role of Wnt signalling in the expression of incentive learning using the conditioned place preference (CPP) paradigm. We hypothesized that inhibition of Wnt signalling with Wnt palmitoylation inhibitor, IWP-2, will dose-dependently affect the expression of AMPH-produced CPP. When IWP-2 was administered into the NAc (0.001, 0.05, 0.5, 1.0 μg/0.5 μl/side) in male Wistar rats during the expression phase of AMPH-produced CPP (20.0 μg/0.5 μl/side), the lowest dose (0.001 μg/0.5 μl/side) did not prevent expression of CPP, while larger doses (0.05, 0.5, 1.0 μg/0.5 μl/side) blocked expression. These results implicate Wnt signalling in incentive learning and DA-mediated behaviours, and suggest its inhibition may affect the expression of AMPH-produced CPP. (Funded by NSERC)

2-F-141 Co-allocation of Appetitive and Aversive Memories in the Lateral Amygdala

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Previous research has revealed a central role for the lateral amygdala (LA) in representing memories of both fear and reward. This ability to store memories of diverse emotional valence raises an important question: how are neurons in the LA able to differentially encode fear and reward memories? One of two general models could account for this capacity: either the amygdala is fully partitioned into valence-specific neural circuits which separately process fear and reward, or there exists a population of amygdala neurons which are able to encode memories of either emotional valence. Here we examine whether neurons in the LA are capable of being involved in fear and reward memory traces. To test this hypothesis, we virally overexpressed CREB and C%2B%2B (a novel blue-light inhibitory opsin) in a random ~10% of principal LA neurons. Prior studies have separately shown that CREB-overexpressing neurons are preferentially recruited into either a fear or reward memory trace. That is, neurons overexpressing CREB are preferentially allocated to an appetitive cocaine-cue reward memory and an aversive Pavlovian tone-fear memory. Here, by training each mouse in both an appetitive and aversive task, we will examine if CREB-overexpressing neurons are allocated to both a rewarding and fearful memory trace. Our findings will shed light on whether the LA is fully partitioned into separate, valence-specific circuits.

2-F-142 Human rGDF-11 counteracts age-related short-term memory impairments in middle-aged mice

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Currently in Canada the number of elderly individuals surpasses the younger population. The effect of cognitive decline due to normal aging is having a growing impact. It has been suggested that cognitive decline begins as early as the mid-30s and only gets worse as age increases. Interestingly, previous work has demonstrated that treating elderly mice (18 months old) with human recombinant growth differentiation factor 11 (GDF-11) leads to enhanced vasculogenesis and neurogenesis in the sub-ventricular zone of the brain, as well as improvement in cognitive ability. The molecular mechanisms mediating this response remain unclear and the potential impact on cognitive rejuvenation in middle age is not known.. The goal of the current research was to determine the impact of GDF-11 on cognitive ability in middle-aged mice (9 month). GDF-11 was administered to both young (1.5 month old) and middle age (9 month old) mice and specific cognitive tests were performed to evaluate outcome on

short-term memory, using standard behavioral tests (y-maze and novel object recognition (NOR)) 24 hours after a single intraperitoneal injection of rGDF-11. Administration of rGDF-11 resulted in increased expression of GDF-11 protein in brain tissue of young, but not middle aged mice treated with rGDF-11. While the potential mechanisms are still under investigation, our results suggest a role for GDF-11 as a potential strategy to circumvent the functional implications of cognitive decline associated with aging. This research was funded by FRSQ (NMJ) and NSERC (PDS).

2-F-143 The Adverse Effect of Auditory Stress on Mice Performance: Impact of Different Type of Stresses and Pregnancy

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The association between maternal prenatal stress and infant birth outcome has been widely documented in animal studies. There is a great body of literature about the negative effects of different kinds of stressors throughout development. However, less information exists about adverse effects of different types of stresses, particularly auditory stress, during pregnancy on mice behavior after pregnancy. To address the impact of different types of stresses during pregnancy on mice performance after it, present study was performed on four groups of female mice including: 1) mice with auditory stress during pregnancy (high intensity 3000 Hz tone), 2) mice with cognitive stresses during pregnancy (restraint and Elevated Plexiglass Platform), 3) mice without stress during pregnancy, and 4) non-pregnant mice with stresses. Performance of these four age-matched groups were compared by some behavioral tests (Elevated Plus Maze, Activity Box Test, Novel Object Recognition Task, and Balance Beam Test) after pregnancy. In this presentation, the negative effects of auditory stress on mice behavior compare to cognitive stress and control groups will be discussed for the first time. The practical message is that the adverse effects of prenatal stresses on mice behavior should take into consideration in both moms and offspring.

2-F-145 Contextual Fear Conditioning in Zebrafish

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Adult zebrafish are a useful vertebrate model organism for studying memory due to their genetic accessibility, low cost, and potential for high-throughput analysis. However, there are few robust, rapidly acquired, one-trial learning paradigms that have been established in zebrafish. Such a paradigm would be useful for facilitating the in-depth analysis of mechanisms involved in memory formation and forgetting. Towards this end, we developed a contextual fear conditioning task in zebrafish. Following an acclimation period, exposure of fish to a series of mild electric shocks results in a reduction in locomotor activity (distance travelled). Upon re-exposure to the conditioning tank a day later, fish continued to demonstrate a decrease in locomotor behavior relative to baseline. Importantly, upon exposure to a tank distinct from the training tank, fish had normal levels of locomotor activity. We believe this paradigm will prove useful in the study of learning and memory due to its robustness and rapid acquisition. Furthermore, the task is similar to the widely used contextual fear conditioning paradigm in rodents, thereby allowing straightforward comparisons to a considerable body of experimental findings. Research support: This work was supported by the Canadian Institute for Health Research (MOP86762) and the Human Frontier Science Program (LT000759/2014).

2-F-146 Striatal Regulation by Acetylcholine and Glutamate Co-transmission

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Cholinergic tonically active neurons (TANs) are neurons thought to be critical for information processing and modulation of the striatum. TANs co-express vesicular acetylcholine transporter (VAChT) and vesicular glutamate transporter 3 (VGLUT3) and thus can store and release acetylcholine (ACh) and glutamate (Glut). Recent studies suggest that the balance between ACh and Glut is critical for controlling striatal-dependent behaviour. We hypothesize that ACh and Glut differentially regulate striatal function, where a balance favouring ACh may facilitate cognition processing and a balance favouring Glut may control reward behaviour. We selectively eliminated VAChT or VGLUT3 in TANs to generate mice with an altered striatal balance of ACh and Glut (D2CreVAChTfx2, D2CreVGLUT3fx2). These mouse lines were tested for behaviours regulated by the striatum and we found that D2CreVGLUT3fx2, but not D2CreVAChTfx2 mice were hyperactive and D2CreVAChTfx2, but not D2CreVGLUT3fx2 mice had an anti-depressive-like phenotype and required more sessions to reach criteria during the reversal phase of the pairwise discrimination and reversal task. These results suggest that ACh and Glut have different impacts on key behaviours regulated by the striatum. Mice unable to release ACh from TANs display reduced depressive-like behaviours and lack cognitive flexibility whereas mice unable to release Glut were hyperactive. Ultimately, our experiments indicate that the ability of TANs to co-release neurotransmitters is critical to regulating the complex and diverse behavioural functions of the striatum.

2-F-147 Behavior, brain serotonin system and pharmacological responses to stimulation of 5-HT1A receptors in recombinant mouse lines with different predisposition to catalepsy

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New recombinant mouse lines - the B6.CBA-D13Mit76C (B6-M76C) and B6.CBA-D13Mit76B (B6-M76B) distinguished by the fragment 110.56-118.83Mbp of chromosome 13 were created. This fragment containing the main locus of catalepsy and the 5-HT1A receptor gene was transferred to a C57BL/6 genetic background from catalepsy-prone CBA and catalepsy-resistant C57BL/6, respectively. B6-M76B mice were non-cataleptic, whereas 14% of B6-M76C mice demonstrated catalepsy. Exploration and locomotor activities were not affected in cataleptic mice, while B6-M76C mice showed decreased depressive-like behavior. Acute administration of 5-HT1A receptors agonist (8-OH-DPAT) produced dose dependent hypothermic reaction in the both lines, while its chronic administration induced desensitization of 5-HT1A receptors in B6-M76C mouse line, but not in B6-M76B. At the same time, chronic 8-OH-DPAT treatment also increased locomotor activity in B6-M76B but not in B6-M76C mice. It was shown 5-HT metabolism was significantly reduced in the hippocampus of B6-M76C mice and this effect was accompanied by increased expression of the 5-HT1A receptor. These changes were accompanied by the decreased expression of key genes belonging to the brain serotonin system in the midbrain. The present study indicates the B6-M76C mice as a suitable model for study the mechanisms underlying different kinds of catalepsy-associated psychopathology. The study was supported RSF grant № 14-25-00038

2-F-148 The Facilitative Effects of Fame on Working Memory

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The default network (DN) is a set of brain regions that are engaged during tasks that are self-referential in nature, or by stimuli that require access to stored representation (e.g., famous faces). The DN encompasses the medial prefrontal cortex, posterior cingulate cortex, lateral and medial temporal lobes, and the posterior inferior parietal lobule. Activity within the DN has been associated with poor task performance, off-task behaviour, and mind wandering. Recent research suggests that the DN can facilitate controlled processing when demands of the task are congruent with the DN, specifically when the task requires access to stored representations (e.g., famous faces; Spreng et al., 2014). This study investigates the role of the default network during controlled processing. Specifically we investigate whether default network activity can facilitate working memory task performance when stored representations are task-relevant. In this study, 25 participants completed a 1-back and 3-back working memory (WM) task consisting of fame-relevant versus fame-irrelevant trials. Results revealed a significant interaction between fame-relevance and WM; the facilitative effects of fame was greater for 3- vs. 1-back conditions. These results demonstrate access to stored representational knowledge can facilitate WM. These findings provide the foundation for a planned fMRI study to investigate the extent to which this facilitation effect is associated with default network brain activity, providing further evidence against conceptualizations of the DN as a 'task-negative' network.

2-F-150 Non-selective neurons contribute information to neuronal ensembles by modifying noise correlation structure

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Neurophysiological studies have identified single neurons selective for the properties of sensory stimuli, behavioral or cognitive, and motor actions. These neurons are intermixed with neurons that do not exhibit any discernable selectivity. It is widely believed these "non-selective" neurons are selective for other properties that are unaddressed in any given task, and as such they are typically excluded from further analysis. Here we show that neurons "not selective" for a task parameter can still increase the amount of information about that parameter in an ensemble of neurons, and achieve this by modifying the structure of correlated firing rate variability (i.e. noise correlations) within the ensemble. We used microelectrode arrays to record the activity of ensembles of multiple neurons in dorsolateral prefrontal cortex of macaque monkeys while they performed a working memory task, and used accepted neurophysiological criteria to determine whether individual neurons were "selective" for task properties. We found that "non-selective" neurons present in an ensemble can increase the amount of task-related information but that these information gains were eliminated when the ensemble's noise correlation structure was perturbed. Our results identify a role for "non-selective" neurons in the coding of information, visible only at the level of neuronal ensembles. More broadly, our results highlight the limitations of the traditional neurophysiological method of examining neurons in isolation, emphasizing the importance of simultaneity and ensemble-level phenomena.

2-F-151 Sharp Wave Ripples during Visual Exploration in the Primate Hippocampus

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Hippocampal sharp-wave ripples (SWRs) are highly synchronous oscillatory field potentials that are thought to facilitate memory consolidation. SWRs typically occur during quiescent states, when neural activity reflecting recent experience is replayed. In rodents, SWRs also occur during brief locomotor pauses in maze exploration, where they appear to support learning during experience. In this study, we detected SWRs that occurred during quiescent states, but also during goal-directed visual exploration in nonhuman primates (Macaca mulatta). The exploratory SWRs showed peak frequency bands similar to those of quiescent SWRs, and both types were inhibited at the onset of their respective behavioral epochs. In apparent contrast to rodent SWRs, these exploratory SWRs occurred during active periods of exploration, e.g., while animals searched for a target object in a scene. When they coincided with target-object fixations during search, detection was more likely than when these events were decoupled. Furthermore, ripples were more likely to occur on repeated than initial image presentations, suggesting an association with memory-guided search. These results reveal that SWRs are not limited to off-line states as conventionally defined; rather, they occur during active and informative performance windows including search on familiar scenes. The SWR in primates is an infrequent but influential phenomenon whose appearance during active search may indicate a new, extended role of SWRs during exploration in primates. NSERC Discovery, CREATE VSA, OGSST, Brain Canada, Krembil Foundation

2-F-152 Synaptic impairment of frontal cortical fast-spiking basket cells induces cognitive and behavioural deficits in mice with a Cacna1a loss-of-function mutation

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Loss-of-function mutations in the CACNA1A gene result in episodic ataxia (EA2) in humans. We investigated 16 patients carrying different CACNA1A loss-of-function mutations and revealed that the majority of them had neurocognitive impairment that includes a spectrum of impulsivity, intellectual deficiency and autism. The mechanisms underlying these deficits are unknown. We previously demonstrated that a deletion of Cacna1a in forebrain GABAergic interneurons (IN) leads to selective synaptic defect of parvalbumin-positive (PV) basket cells and induce epilepsy in mice. Such impairment of perisomatic inhibition from PV-IN dysfunction in neocortical circuits might also induce cognitive deficits in Cacna1a mutants. To investigate whether a functional impairment of PV IN contributes to these cognitive deficits, we used mice carrying a targeted heterozygous deletion of Cacna1a restricted to PV neuronal populations (PVcre;Cacna1ac/+). We show that this mutation impairs perisomatic inhibition onto pyramidal cells in the orbitofrontal cortex (OFc). We observed that the haploinsufficiency of Cacna1a in PV-IN leads to impulsivity and reduced cognitive flexibility in PVcre;Cacna1ac/+ mutant mice. These deficits are recapitulated by AAV-Cre injections in the OFc of Cacna1ac/+ mice suggesting a critical involvement of orbitofrontal circuits. Our results demonstrate that the haploinsufficiency of Cacna1a leads to significant cognitive deficits in humans and in conditional mutant mice, and that this is partly attributable to a disturbed perisomatic inhibition in the orbitofrontal circuits.

2-F-153 Differential Effects of Dopamine Antagonists on Cognitive Performance in Healthy Controls

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Dopamine (DA) plays an important role in attention, memory, and learning. Evidence has shown that the optimal levels of DA that facilitate cognitive performance are differentially dependent on the activation of D1 and D2 receptors in the striatum and prefrontal cortex. Given the predominance of D1 over D2 receptors in prefrontal cortex, it would be hypothesized that the selective blockade of D1 receptors should more strongly impair frontal executive function. To test this hypothesis, we have administered D1 and D2 receptor antagonists to healthy monkeys while they performed cognitive tasks on a touch screen. One of two DA receptor antagonist drugs (SCH 23390 hydrochloride: a D1/D5 antagonist or Eticlopride hydrochloride: a D2/D3 antagonist) or placebo was administered to each monkey prior to each test session. Four tasks were tested: (1) 'visually guided reaching', which tests reaction time and accuracy, (2) 'reversal learning', which tests association learning and attention, (3) 'spatial ordered sequential search' which tests spatial working memory, and (4) 'delayed match to sample' which tests object working memory. Metrics from these tasks were compared between the control and drug conditions. Results show that both the D1/D5 and D2/D3 antagonists increased reaction times and decreased motivation. In the reversal learning and delayed match to sample tasks, the D1/D5 antagonist also resulted in a small improvement in cognitive performance. These results provide insight into the relationships between DA pathways and cognitive performance.

2-F-154 Placebo Analgesia in a Chronic Neuropathic Pain Model in Mice

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The placebo effect constitutes a powerful mechanism for patient recovery. Human studies have become to identify key brain areas and mechanisms associated with the placebo effect; yet, an animal model of placebo analgesia (the most robust type of placebo effect) remains elusive. In order to further understand the neural substrates of placebo analgesia, we attempted to develop a model of placebo analgesia in mice. : Chronic neuropathic pain was induced using the spared nerve injury (SNI) model. Seven days after this surgery, each mouse underwent a 4-day conditioning procedure in which an active analgesic drug, morphine (10mg/kg), was associated with two cues: Plexiglas cubicles (contextual) and handling/injection (tactile). On the following test day, half of the mice received its vehicle (saline) and the other half received naloxone. Mechanical allodynia was measured on all five days using a set of von Frey filaments. During the conditioning phase, mice experienced significant morphine analgesia. On test day, mice that received saline experienced significantly elevated pain tolerance (i.e., placebo analgesia), which peaked at 5 minutes post-injection and persisted for three hours. Naloxone reversed the placebo analgesia, as the withdrawal thresholds of naloxone-treated mice did not differ from baseline measures of post-SNI. These results reveal a successful and novel development of a mouse model of placebo analgesia, specifically for chronic neuropathic pain. Further, it supports the involvement of the endogenous opioid system in placebo analgesia found in humans.

2-F-155 Increased Glucocorticoid Receptor Activity in the Medial Prefrontal Cortex Prevents the Expression of Empathy in Mice

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Empathy has deep evolutionary roots. It is a fundamental process for social behaviour and allows the understanding of emotions by sharing sensory and affective states with other individuals. It is also susceptible to blockade by social stress. Here, we sought to uncover the neurobiological mechanisms by which stress prevents empathy using a rodent model of empathy with pain as a stimulus. We assessed pain behaviour in mice that were tested either in isolation or in dyads (with a cagemate or stranger) wherein one or both mice were injected with 0.9% acetic acid (10 ml/kg, intraperitoneal). Following behaviour, mice were sacrificed and their brains removed. The brain was then microdissected and brain areas known to be involved with empathy were isolated (medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC)) as well as important regulators of the stress response including the bed nucleus of the stria terminalis (BNST) and the paraventricular nucleus of the hypothalamus (PVN). We then assessed whether glucocorticoid receptor (GR) activity was altered in these brain regions. We find that mice that do not engage in empathy behaviours have increased phosphorylation of the GR in the mPFC, but not the other examined brain regions. We suspect that an increased stress response prevents the expression of rodent empathy in unfamiliar mice through a mechanism that involves glucocorticoid receptor expression in the mPFC.

2-F-156 Recovery of memory in mice that model Alzheimer's disease

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The clinical hallmark of Alzheimer's disease (AD) is a progressive decline in cognitive function. Substantial evidence indicates that b-amyloid (Ab), which is widely implicated in AD, disrupts synaptic function, possibly by promoting excessive internalization of postsynaptic AMPA-type glutamate receptors (AMPARs). These findings suggest that the memory deficits described both in patients affected by early AD and mouse models of AD may be due to high levels of Ab promoting the loss of postsynaptic AMPAR. Here we directly tested this hypothesis.. We found that increasing Ab either acutely or chronically in mouse model of AD (TgCRND8, 5xFAD, HSV viral injection of mutated APP) disrupts both consolidation and reconsolidation of memory measured in hippocampal dependent tasks (context fear conditioning and water Maze). Preventing AMPAR endocytosis during memory encoding restored the ability of both acute and chronic mouse models to form new memories (consolidation). Remarkably, preventing AMPAR endocytosis during a memory reminder enabled the recovery of an otherwise inaccessible old memory (reconsolidation) in AD mouse models. These findings elucidate the disruptive role of Ab in synaptic function and raise the possibility that restoring plasticity during memory encoding and/or retrieval by targeting the loss of postsynaptic AMPAR may help support the ability to form new memories as well as enable recovery of lost past memories in AD patients.

2-F-157 Lateral Occipital Complex activation in response to repetitive visual stimuli in People with Migraine Headaches

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Migraine is a disabling neurological disorder that affects 24.8% of women and 8.2% of men in Canada. Impaired habituation to repetitive visual stimuli is a mechanism integral to interictal migraine (in between headache events). For example, using event-related potentials with EEG scalp-recordings, migraineurs show increased brainwave amplitudes across trial blocks during presentation of repetitive

complex visual stimuli. In this study, we used functional magnetic resonance imaging (fMRI) to assess the neural networks of this lack of cognitive habituation in migraineurs to repetitive visual stimuli. The lateral occipital complex (LOC) has been shown to have a reduction in haemodynamic response with stimulus repetition. We predicted that controls would have habituation of this region across trial blocks while viewing repetitive visual stimuli and migraineurs would lack this habituative response.By contrasting the first five blocks to the second five blocks we found habituation responses in regions of the lateral occipital complex (LOC) in both migraineurs and non-migraine controls. Specifically, the migraineurs revealed habituative responses in the more dorsal caudal (LO) portion of the LOC while controls showed increased habituation response in the more ventral occipito-temporal cortex (VOT). Given the role of the LOC for processing visual form in general and categorization specifically, these findings support recent findings that visual processing effects in migraine go behind the sensory response.

2-F-158 Inducible rescue of NMDA receptor deficiency to measure the plasticity of neural networks in a model of schizophrenia

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Neurodevelopmental disorders like schizophrenia present challenges for treatment because diagnosis occurs decades after the causal insult to the CNS. It's not clear whether current treatments fail because the neural circuits that mediate schizophrenia-relevant behaviours are unable to overcome developmental deficits in wiring. We addressed this question by generating a new mouse line in which NMDA receptor (NMDAR) hypofunction occurs throughout development, and is rescued postnatally. NMDAR levels and physiology were compared in WT, NR1 knockdown, and NR1 rescue mice (see Islam et al. poster for molecular, see Binko et al. poster for electrophysiology). We discovered sociability, cognition and executive function were normalized in NR1 rescue mice, similar to wildtype levels. Thus, treatment-resistant cognitive and negative symptom endophenotypes respond well to postnatal interventions. Locomotor activity and stereotypy were partially improved, suggesting less plasticity of these behaviours. Surprisingly, there was no benefit to early intervention at adolescence; similar effects on behaviour and biochemistry were observed when NMDAR were restored in adulthood. This suggests sufficient neural plasticity is present in adulthood to allow for reversal of behavioral abnormalities in this well-validated model of schizophrenia. Even partial restoration of NMDAR levels can improve endophenotypes of positive, cognitive, and negative symptoms of schizophrenia. The goal of effective treatment in adulthood for negative and cognitive symptoms of schizophrenia is therefore realistic.

2-F-159 Effect of sexual experience on the rewarding state induced by mating in the female rat.

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It is well established that, when giving the opportunity, female rats control the rate of sexual stimulation. This capacity to control or pace the sexual interaction induces a reward state as evaluated by conditioned place preference (CPP). The rewarding state induced by mating has been observed in sexual naive females. The aim of the present study is to determine the effect of 10 sessions of sexual behavior, paced and non-paced, on the reward state induced by mating. Wistar female rats were

ovariectomized and randomly assigned to one of the following groups: 1) Females allowed to pace the sexual interaction 2) Females not allowed to pace the sexual interaction and 3) Females exposed to a sexually experienced male without the possibility of physical contact. Subjects were injected with estradiol (25µg) and progesterone (1mg) 48 and 4 hours, respectively, to induce receptivity. All subjects were tested once a week for 7 consecutive weeks according to their corresponding group. For sessions 8, 9 and 10 groups were subdivided and tested once a week or every 2 days as a CPP´s reinforcements. The results show that the reinforcement interval of every five days produces a rewarding state in both the pacing and no-pacing groups. On other hand, with the two days reinforcement interval no rewarding state was observed. These results suggest that the rewarding state induce by mating depends on the sexual experience and the reinforcement interval. Acknowledgements: technical support Francisco Camacho. Supported by DGAPA IN210215 and CONACYT 167101.

2-F-160 Dissociable roles of GADD45α/ß in the rat perirhinal cortex and hippocampus for object memory: Different forms of DNA methylation?

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DNA methylation and demethylation are necessary for long-term memory (LTM) in various brain regions, including the hippocampus (HPC); however, the role of these epigenetic mechanisms in perirhinal cortex (PRh), a structure critical for object memory, has not been characterized. Using siRNAs, we have assessed the effects of selective DNA methyltransferase (DNMT) and growth arrest and DNA damage-inducible 45 (GADD45) inhibition in HPC and PRh on object-in-place (OiP) memory; this task requires the HPC to processes the spatial location of objects and PRh to process object identity. We also measured learning-induced changes in DNMT and GADD45 mRNA expression following OiP learning. We previously demonstrated a double dissociation between the necessity of de novo methyltransferase, DNMT3a, and maintenance methyltransferase, DNMT1, in HPC and PRh, respectively. We have found the involvement of GADD45α/ß to also be dissociable, as GADD45ß was up-regulated in the DG of the HPC following learning, and only GADD45ß siRNA in the HPC impaired LTM; in contrast, expression of GADD45α and GADD45ß mRNA was enhanced in PRh following learning, and only GADD45α siRNA impaired LTM in this region. Collectively, these findings indicate that different forms of DNA methylation, and possibly demethylation, are required for different mnemonic processes (spatial vs object identification) in different brain areas. Using ChiP-seq and MeDIP analyses, we are currently investigating the functional interplay between GADD45α and DNMT1 on specific gene targets in PRh-mediated object memory consolidation.

2-F-161 Hyper-activation of Right Inferior Frontal Gyrus in Pediatric Obsessive-Compulsive Disorder during a Mental Flexibility Task

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Pediatric Obsessive-Compulsive Disorder (OCD) is a childhood condition that is characterized by mental obsessions and behavioural compulsions. Various executive cognitive impairments are associated with the disorder, including deficits in mental flexibility. Mental flexibility involves the ability to modify mental processes and behaviours in an efficient and continuous manner, thereby facilitating dynamic

engagement with the outer world. FMRI studies have been equivocal in determining the neural correlates of mental flexibility in OCD, and we suggest that using a high temporal and spatial resolution functional neuroimaging modality, such as magnetoencephalography (MEG) would be helpful. Thirty-one children (20 OCD; mean age: 10.75yrs) completed a mental flexibility task in a 151-channel whole-head MEG. 3-D spatiotemporal brain activation maps were created using SPM beamformer source reconstruction. The between-group MEG results revealed greater activation ($p = 0.002$) in the right inferior frontal gyrus (iFG) in the OCD group, in the 150-200ms post-stimulus window, corresponding to peak-activation times across both groups. Activation of the right iFG has been shown to be important in inhibition processing, a key component in mental flexibility. These findings suggest that the OCD group require greater activation of the iFG to achieve average performance levels. These results are the first using MEG to examine mental flexibility in children with OCD, and are consistent with the literature suggesting aberrant function in the prefrontal areas for individuals with OCD.

2-F-162 The spatio-temporal dynamics of "Theory of Mind" in school age children born very preterm

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Very preterm birth (<32 weeks gestation age) has been implicated in social and cognitive deficits that persist through to adulthood. The neural bases for these social deficits have not been examined. In the current study, we used magnetoencephalography for its excellent spatial and temporal resolution to assess Theory of Mind; the ability to understand the mental states of others and to predict their behaviour. We measured false belief understanding -a component of Theory of Mind that describes the ability to understand that others' beliefs can be incongruent with reality- in 24 very preterm born (VPT) school age children (7-13 years) compared to 24 full-term (FT) children. Our findings suggest that VPT children are successful on the ToM task by employing temporal regions from 100-500 ms, such as the inferior temporal gyrus, the right temporal pole and the middle temporal gyrus, without recruiting classic ToM regions such as the temporo-parietal junction (TPJ) or key frontal structures. FT children recruited the TPJ as early as 200 ms in addition to frontal, temporal and parietal regions. We suggest that VPT use a different strategy that relies on the inferior and temporal gyri in inferring mental states, consistent with the atypical functional organisation in the brain.

G – Novel Methods and Technology Development

2-G-163 Counting all possible neuronal circuits for input-output data

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Neuroscientists often measure electrophysiological signals entering and exiting neuronal networks while having no direct access to the intermediate networks that process those signals. For instance in pain research, the activity of both afferent fibres and projections neurons can be recorded while the circuit formed by the interneurons of the spinal cord remains unknown. A natural question is then to evaluate the number of the hidden networks that could explain the input-output data. By using mathematical tools from combinatorics, such as Pólya's theorem, we enumerated all possible networks for which: (1) the network contains distinguishable input and output neurons as well as partially distinguishable interneurones; (2) all connections are directed and for each pair of neurons, there are at most two

connections; (3) input neurons send connections but don't receive any while output neurones receive connections but don't send any; (4) every interneuron receives a path from an input neuron and sends a path to at least one output neurons; and (5) input neurons don't send direct connections to output neurons. We first obtained the generating function for the number of such networks and then used it to obtain precise estimates for the number of networks. Finally, we developed a computer algorithm that allows us to generate all neuronal networks that satisfy the above conditions.

2-G-164 Analysis of apoptotic cell death contribution in Caspase-3 null mice using an endothelin-1 model of cerebral ischemia

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Stroke represents one of the leading causes of long-term disability and death in North America. The failure of a number of recent human clinical trials aimed at enhancing stroke therapy have highlighted the need for developing more accurate, defined and anatomically comparable models of stroke between mice and humans. Thus, we describe here a method of stereotactic microinfusion of endothelin-1 to defined territories of the cerebral cortex in mice. As indicated from the results, source-centered stereotactic diffusion of endothelin-1 from cortical infusion sites allows for regulated induction of vasoconstrictive hypoxia within the cortex in a reproducible and geometrically well-defined manner. This approach confines the zone of injury to the cerebral cortex and exhibits reduced infarct sizes, thus representing what is typically seen in human clinical strokes more accurately. Additionally, cellular and molecular analyses have demonstrated that neuronal injury following ischemic stroke contains both apoptosis and necroptosis in combination with hypoxia-induced necrosis. In order to understand the mechanisms which regulate these forms of cellular injury, we have examined the development of such cerebral infarcts in mice lacking caspase-3. Analyses of endothelin-1 treatment in Casp3 null mice demonstrate a significant protective effect against apoptotic cell death, where injuries were reduced by more than half the wild-type values. These studies thus define this alternative model of cerebral ischemia and demonstrate the extent of apoptotic contribution in the observed injuries.

2-G-165 Parametric modelling of oscillatory sources in MEG

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The cortical sources of oscillatory activity recorded with MEG (magnetoencephalography) are commonly estimated using techniques that result in distributed maps of source strength across a large space (e.g. beamforming or minimum-norm). The goal of many MEG studies, however, is to interpret these maps as a limited set of activated regions, requiring detection of local peaks. Fieldspread, differences in source amplitude or extent can make it difficult to identify distinct spatial sources in this workflow. Parametric source models explicitly search for a sparse source model as a limited set of equivalent current dipoles or multipoles. These techniques have so far been mainly developed for mapping average event-related fields. Here we apply and extend subspace scanning methods as efficient solution for the parametric modelling problem of oscillatory sources, both on the single-subject and on the group level. The procedure consists of computing a low-dimensional signal subspace, scanning this subspace for dipolar or multipolar sources and mapping these on the cortex as equivalent cortical patches. We present new solutions for several experimental questions, namely contrasts, coherence with reference signals, or SNR of oscillatory with respect to broadband activity. We additionally show that the current multipole

formalism can serve as a useful spatial basis for local spatiotemporal wave-like activity. The performance of the proposed methodology is demonstrated using realistic simulations, MEG recordings of spontaneous activity and visually induced gamma oscillations.

2-G-166 A probabilistic approach to identifying cerebrovascular differences between mouse strains

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Different strains of mice are commonly used in a wide range of research areas such as stroke, neurodevelopmental, and cerebrovascular diseases. However, the differences of cerebrovasculature in these common strains remain largely unknown due the complexity of these systems. As a result, comparing the outcomes of studies that have used different strains of mice is currently impractical. We have imaged the complete cerebrovascular network of four common mouse strains, C57Bl/6 (n=10), CD-1 (n=8), 129/Sv (n=8) and CBA (n=9), with high-resolution micro-CT. The vasculature is automatically segmented and represented as an attributed graph where each vessel segment is an edge in the graph with attributes such as diameter, length and direction of that vessel. Each vessel in each sample is annotated with its corresponding anatomical label using these features and a manually labelled dataset in a Bayesian framework. Then, the posterior probability of true labels for each vascular network is calculated assuming a Gaussian distribution on each feature of each label. A high deviation of a label in a sample from the population is highlighted by low posterior probability. The highlighted vessel segments are then studied individually to find the variant features. The known variations of the circle of Willis among these four strains have been successfully highlighted by this method, as well as previously unknown variations in the venous system. This probabilistic framework can be a basis for comparison of the cerebrovascular systems in common mouse strains.

2-G-167 Examination of Drosophila Eye Development with THG microscopy

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Third harmonic generation (THG) microscopy is a valuable imaging modality that can be used to reveal structural information in a biological system without staining. THG signal can be observed at an interface between two different refractive indices or third-harmonic susceptibilities and is augmented in the presence of molecules with long carbon chains. Previous studies have established that carotenoid compounds are ideal for THG microscopy. We therefore sought to determine whether THG from endogenous carotenoid-derived compounds, such as retinal in photoreceptors, could serve as a platform to develop THG miscroscopy for developmental studies. We used the developing compound eye of Drosophila melanogaster as a model system because of its well-known anatomy, and the availability of genetic tools. The Drosophila eye contains 750-800 ommatidia, each housing photoreceptor neurons that utilize the visual pigment rhodopsin, G-protein coupled receptor containing retinal, for photo-transduction. In the first series of observations THG microscopy was shown to be an effective tool for monitoring normal photoreceptor development. We then used dietary restrictions or genetic alleles that perturb rhodopsin expression which causes membrane atrophy, resulting in photoreceptor degeneration. The results demonstrated that THG microscopy can detect rhabdomere degeneration earlier than fluorescence microscopy. THG intensities measured throughout pupal

development showed a distinct age-dependent curve, which changes in the absence of rhodopsin. In conclusion, THG microscopy can be used to monit

2-G-168 A novel approach to assess neurovascular patterning and remodeling in the mouse brain

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Cerebrovascular insults or failures compromise the brain's fragile equilibrium, favoring the onset and/or progression of neurological disorders such as stroke, vascular dementia, or Alzheimer's disease. Given the lack of effective treatments for these conditions, there is an urgent need to better understand how brain blood vessels normally form, function, renew, but also how they respond to injury. Motivated by our scant understanding of the basic principles underlying cerebrovascular maintenance and plasticity, we developed an approach that combines neuroanatomical imaging with computational tools to simultaneously analyze vascular and neuronal modules in their 3-dimensional (3D) environment. Following confocal imaging of immunostained brain sections, our computational method allows for unbiased and automatic quantifications of vascular density and branching, as well as neuronal patterning. Our algorithms can represent these data as histograms, 3D heat maps, or profile plots. For example, data obtained in the healthy adult mouse cerebral cortex (wild-type, n=20; 10 females, 10 males) demonstrate a microvascular density of 2205 ± 54 mm/mm³ (2285 ± 63 in females, 2125 ± 82 in males) and a number of vessel branching points of 60935 ± 2500 branches/mm³ (63752 ± 3280 in females, 58119 ± 3840 in males). No difference was evidenced between genders ($p>0.05$). We are now applying this method to preclinical mouse models of cerebrovascular disorders to characterize the time course of neurovascular remodeling in disease contexts, a crucial step in the quest for therapeutic targets.

2-G-169 Low profile halo head fixation in non-human primates

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We present a new 'halo' technique for head fixation of non-human primates. Our aim was to create low profile system that would maximize the area of the skull available for cranial implants for electrophysiological experiments. The design incorporates sharp skull pins that are directly threaded through a low set halo frame and are seated into implanted titanium foot plates on the skull. The inwardly directed skull pins provide an easily calibrated force against the skull. This device allowed for head fixation within 1 week after implantation surgery. Care of the halo involved routine cleaning and pin tightening as required. The halo was stable in 2 animals for the 4-6 months of testing. The quality of single unit neural recordings collected while using this device to head fix was indistinguishable from traditional acrylic based head-post fixation. The halo could be easily taken off the permanently implanted foot plates and later put back on. The foot plates used in this system did not result in significant MRI distortion in the location of deep brain targets (~0.5 mm) of a 3D printed phantom skull. In comparison with existing methods of halo fixation, the low profile design allows greater access to the majority of the frontal, parietal, and occipital skull. It has fewer parts and can hold larger animals than previous halo designs. Given the stability, simplicity, immediate usability, and low profile of this head fixation device, we propose that it is a practical and useful means for performing electrophysiological recording experiments on non-human primates.

2-G-170 Opto-Panx1: Engineering a new optically controlled Pannexin 1 channel

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Pannexin 1 (Panx1) forms a large pore ion channel that regulate a number of cellular and (patho)physiological processes including ATP release, phagocyte chemotaxis, inflammasome assembly and neuronal excitotoxicity. Characterization of Panx1 has expanded over the past decade, but pharmacological and genetic manipulations of the channel have been enigmatic due to overlapping targets for antagonists and compensation by other Panx isoforms. Here, we have developed a new optogenetic tool for the isolation and study of Panx1 signaling, opto-Panx1. Opto-Panx1 consists of a two-protein system. We engineered an optically-activated Hepatitis C Virus protease (HCVp) by inserting a photocleavable protein (PhoCl) between HCVp and an inhibitory peptide. Next, we mutagenized the caspase cleavage site in the Panx1 C-tail to a consensus HCVp site (Panx1-HCV). Proteolytic truncation of the Panx1 C-tail opens the channel pore. We assessed the functional status of opto-Panx1 by TO-PRO-3 dye uptake and electrophysiology. Photostimulation of opto-Panx1 promoted dye uptake and increased whole cell currents in Neuro2a cells but not cells expressing a non-cleavable mMaple-HCVp variant. Cell blebbing was also evident, consistent with reported Panx1 activities in apoptotic cells and ischemic neurons. No response was observed in cells solely expressing PhoCl-HCVp or Panx1-HCV. For in vivo applications, we generated a bi-cistronic AAV vector for dual expression of PhoCl-HCVp and Panx1-HCV with a proximal floxed DsRed-STOP codon element allowing Cre recombinase-driven expression.

2-G-171 Application of Support Vector Machines to Longitudinal Functional Neuroimaging Data

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Introduction Trends in brain activity, like activity related to attention and memory, can impact a person's daily life for the better or worse. High dimensional longitudinal neuroimaging data (HD-LND) provides insight into these trends, but analysis is challenging. Unlike cross-sectional data, temporal correlation and heteroscedasticity complicate analysis. The longitudinal support vector machine (LSVM) can differentiate trends by separating data with a hyperplane while assuming that there is a longitudinal temporal component. I used an LSVM to handle the complexity of HD-LND magnetoencephalography data, classifying whether it indicates an externally measurable trend (like deteriorating function). Methods To validate the LSVM method, I compared classification accuracy across exemplars relative to standard classifiers (SVM, Logistic Regression). Exemplars include simulated longitudinal trends, these trends added to resting MEG data, and actual longitudinal data. Results The LSVM performed better than standard classifiers on data with a temporal trend and increasing noise. No advantage existed where there was no temporal trend. The output of the LSVM can be interpreted to determine which dimensions of the HD-LND drive accurate classification over time. Conclusions The LSVM provides researchers additional insight into the evolution of brain activity by having explicit temporal components. Compared to non-temporal methods, the LSVM had higher classification for noisy longitudinal data. This leads to the LSVM being a promising technique for analysing HD-LND.

2-G-172 Single-Cell Optical Control with a Digital Multi-Mirror Device

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The nervous system translates sensory information into spikes using the "neural code", i.e. the code that determines how information is captured by different patterns of spikes. The neural code ultimately underlies all of our perceptions, and thus, cracking it is a major goal in neuroscience. To test hypotheses about the neural code with causal experiments, one must control spikes in many individual neurons simultaneously. However, this requires a level of spatial and temporal resolution that is beyond current tools. Here, we aim to address this technical gap for ex vivo experiments using a combination of optogenetics and a Digital Multi-mirror Device (DMD). A DMD is a chip that contains hundreds of thousands of small mirrors that can rapidly be set to reflect light onto a specimen. We verified the use of the DMD to elicit reliable spikes optogenetically with high temporal precision. We then examined spiking in both "targeted" and "non-targeted" neurons, by examining spiking activity and postsynaptic potentials triggered while varying the intensity, size, and location of DMD illumination. We show that at the right level of intensity, with a sufficiently small spot focused on a neuron's soma, we can control spiking activity in an individual cell. Thus, we demonstrate that, a DMD can be used to optically control spiking in individual neurons. Future studies will be able to use this technique to test hypotheses about different neural codes.

2-G-173 Micropillar arrays selectively coated with humidified microcontact printing reveal cue-dependent traction forces and molecular recruitment within single cells

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Cells navigate through a complex extracellular matrix (ECM) and exert mechanical force via engagement to proteins in the ECM. To study this mechanism, in vitro sensors have been developed to quantify cell traction forces, but no force measurements of single cells responding to multiple patterned cues have been reported. Here, we combine humified microcontact printing, a high resolution surface patterning technique, and micropillar array detector devices (mPAD). This novel combination of techniques allows us to measure traction forces of single cells for two juxtaposed cues. We demonstrate that cell traction forces vary based on the adhesivity of the surface and correlate with focal adhesion density. Additionally, we see that traction forces redistribute based on the adhesivity difference between cues presented side by side. Function blocking assays were performed to further elucidate the contributions of receptor recruitment to the mechanotransductive response. Through these studies, we have further characterized the role of integrin-β1 in the cellular response to the protein netrin-1 and investigated novel co-receptor interactions. The presented work demonstrates that the developed sensor is a valuable tool in both understanding the cellular response to a multi-cue environment and for initiating studies aimed at a deeper understanding of mechanotransduction.

2-G-174 Advances in Fiber-based Tissue Identification for Electrode Placement in 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 as well as blood vessels, in vitro, in human brain samples and in vivo, in rats. We have also repeated the in vitro procedure with the probe inserted in a DBS stimulating electrode and found the results were in good agreement. We are in the process of using this procedure on in vivo primate specimens undergoing DBS electrode implantation. Furthermore, we are validating a second fiber optic device, with micro-optical components, that will result in label free, molecular level sensing capabilities, using CARS spectroscopy. The final objective will be to use this data in real time, during deep brain stimulation neurosurgery in humans, to increase the safety and accuracy of the procedure.

IBRO – International Brain Research Organization

2-IBRO-175 Differential expression of Sox2 in two models of adult neurogenesis

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Introduction Sox2 is one of the transcription factors ensuring the proper function of adult neural stem cells. Sox2 deletion in mice results in a loss of adult hippocampal neurogenesis. Moreover Sox2 is one of the four pluripotency-inducing genes leading to induced pluripotent stem cells. Pleurodeles Amphibians are one of the precious models of adult neurogenesis due to their high ability of regeneration in the CNS - especially the spinal cord. Aim of the work We addressed the mechanism by which Pleurodeles are able to guarantee adult neurogenesis in the CNS more efficiently than Mammals, by comparing Sox2 expression between Pleurodeles and sheep in the caudal brain stem (area postrema) which is phylogenetically conserved in all vertebrates. Method Sox2 expression was assayed by RT-qPCR on RNA from microdissected tissues of Pleurodeles brainstem and sheep neurogenic niches, and from EGF/bFGF-expanded neurosphere cultures of sheep brain. From all these biological samples, RNAs were extracted by TRIzol, then reverse-transcribed into cDNA that were subjected to qPCR with SyBr-Green. In sheep brainstem, Sox2 was assayed by immunohistochemistry. Results Sox2 was found expressed in tissue and neurospheres of caudal brainstem, both in sheep and Pleurodeles. Sox2 expression was not detectable though in primary, non-renewable cell masses from dorsal subventricular zone of sheep. Conclusion We could conclude that Sox2 expression is essential for proper function of neural stem cells, especially self-renewal, in both Amphibian and Mammalian brains.

2-IBRO-176 Stress effects and serotonin 4 receptors in mouse Central nervous system

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Adaptive decisionmaking to eat is crucial for survival but in neurodegenerative and mental diseases, the brain persistently supports persistent changes in food intake. How the brain persists in reducing or enhancing food intake to the point of death despite the evolution of multiple mechanisms to ensure survival by governing adaptive eating behaviors in front of stress remains mysterious. In order to study the functions of 5HTR4, we previously engineered the 5HTR4 knockout mice and evidenced their critical role in anorexia-like and binge eating. An absence of increase in pCREB/CREB ratio was found in the

hypothalamus of stressed 5-HTR4 KO mice, suggesting potential disruption of gene expression . Using transcriptome and RQ-PCR analyses, new influences of the 5-HTR4 of hypothalamic targets involved in neurogenesis and in DNA methylation were found in stressed mice, suggesting that 5-HTR4 could induce persistent morphological changes of neurons and favor a persistent restrictive food intake. Consistently, we found that 5-HTR4 exert a positive control of the anorectic brain-derived neurotrophic factor in the medial prefrontal cortex, in which 5-HTR4 control stress-induced anorexia. The number of dendritic spines of pyramidal cells in the medial prefrontal cortex is reduced in the absence of 5-HTR4, which may support the abnormal resistance of KO4 mice to chronic stress-induced hypophagia. The present study shows that 5-HTR4 may contribute to implement neural networks by controlling gene expression of neural growth factors that are involved in adaptive behavior to stress.

2-IBRO-177 The anxiolytic-like effect of cannabidiol in chronically stressed mice is mediated by the endocannabinoid system: role of neurogenesis, autophagy and dendritic remodeling

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Repeated injections of cannabidiol (CBD) attenuate the anxiogenic-like effects induced by Chronic Unpredictable Stress (CUS) through neuroplastic changes. We investigated if the behavioral and pro-neurogenic CBD effects in stressed mice are mediated by CB1, CB2 or 5HT1A receptors. We also evaluated the drug effects on dendritic remodeling and synaptic proteins expression, as Synapsin Ia/b, mGluR1 and PSD95, as well as on the expression of FAAH, GSK3β and autophagy-related proteins mTOR, LC3B and Beclin-1. C57/BL6J mice were allocated in non-stressed groups or submitted to CUS during two weeks, receiving daily combined injections (i.p.) of vehicle, WAY100635, AM251 or AM630, followed by vehicle or CBD. At the end of the procedure mice were submitted to behavioral tests and the hippocampus was dissected to perform immunolabeling, Western Blot or Golgi techniques. CBD induced anxiolytic-like responses in stressed animals accompanied by an increase in hippocampal neurogenesis, dendritic remodeling and autophagy induction. Moreover, CBD decreased FAAH and increased p-GSK3β expression. The anti-stress CBD effect was prevented by pre-treatment with AM251 and AM630, but not WAY100635. The two antagonists also attenuated the pro-neurogenic effects of CBD in distinct ways. Furthermore, AM251 attenuated the CBD responses on autophagy, and AM630 on GSK3β expression. These results suggest that CBD prevents the behavioral effects induced by CUS through CB1 and CB2 receptor activation, which could recruit intracellular pathways involved in neurogenesis, autophagy and dendritic remodeling.

2-IBRO-178 Manganese-induced DAergic toxicity is reduced in trt-1 mutation of Caenorhabditis elegans

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Background: Exposure to manganese (Mn) is an environmental risk factor for Parkinson's disease. Recent evidence suggest telomerase reverse transcriptase (TERT), participate in non-telomeric functions and may play a role in protection of cells from oxidative stress and DNA damage. Hence, the study investigated the effects of Mn toxicity in trt-1 mutation of C. elegans, with a view to assess the role of this gene in DAergic degeneration following Mn-induced Parkinsonism. trt-1 is the catalytic subunit of

telomerase in C. elegans. Methods: Wild-type (N2) and trt-1 mutants (YA1059) worms were exposed to Acute Mn treatment for 1 hour at L1 stage. Controls were treated in 85 mM NaCl; vehicle for Mn. Survival assay and behaviour (Basal slowing response, chemotaxis) were assessed. DAergic degeneration was evaluated in successful crosses of trt-1 worms with dat-1::GFP (BY200) worms. Results: The present study showed that trt-1 worms are less sensitive to Mn-induced lethality compared to wild-type (wt) worms. Mn induces DAergic degeneration in wt worms but surprisingly, not in trt-1 worms. Basal slowing was altered in both wt and trt-1 worms, however trt-1 worms improved significantly than wt worms. Mn treatment did not affect chemotaxis by NaCl in both wt and trt-1 mutants worms. Conclusions: trt-1 may play a role in accumulation of Mn in C. elegans. Alterations of telomeric functions by mutation of trt-1 may result in adaptability to Mn induced toxicity. Plasticity by NaCl chemotaxis may be controlled by other neurotransmitter signaling other than dopamine in C. elegans.

Wednesday, June 1, 2016

A - Development

3-A-1 A heterosynaptic mechanism controls axon branch dynamics in the Xenopus laevis visual system

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The developing retinotectal system of albino Xenopus laevis provides a useful model to study the influence of activity-dependent mechanisms on axon dynamics as it is amenable to time-lapse imaging in the unanesthetized intact animal. Retinal ganglion cells (RGC) in the Xenopus tadpole normally project all their axons to the contralateral optic tectum, but in a small fraction of animals, one or two RGC axons are instead misguided ipsilaterally. Using in vivo two-photon microscopy, we observed changes in branch dynamics of such ipsilateral RGC axons during the presentation of flashes of light directed into either the ipsilateral or contralateral eye, thus stimulating either the single ipsilateral axon or its neighbouring contralateral inputs respectively. We found that contralateral, but not ipsilateral, eye stimulation was sufficient to increase branching of the single ipsilateral axon. This finding implicates a non-cell-autonomous mechanism that promotes activity-dependent axonal elaboration in response to increased activity of surrounding contralateral axons, presumably cooperatively acting to drive postsynaptic firing of tectal neurons. Stimulation of the specific axon by itself was not sufficient to enhance its growth. However, we find that firing of the ipsilateral axon did upregulate the rate of branch tip retractions. This finding confirms that the pattern of visual stimulation plays an instructive role in mediating changes in branch dynamics and that heterosynaptic mechanisms promote axon elaboration and extension.

3-A-2 The RNA-binding protein Musashi2 regulates asymmetric neural precursor cell divisions of the developing cerebral cortex

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The brain's complex circuitry is generated through asymmetric cell division (ACD) of neural precursor cells (NPCs) within the developing cerebral cortex. These divisions produce one NPC as well as one differentiated neuron, allowing for simultaneous NPC renewal and cortical expansion. ACD takes place,

in part, due to mRNA localization to a single region of the dividing cell. Since protein synthesis should not occur until division is complete, mRNA localization is likely coupled with translational repression. A potential mediator of this process in NPCs is the RNA-binding protein Musashi (Msi2), as Drosophila Msi represses translation to guide the formation of mechanoreceptor neurons and glia. We are therefore investigating the role of Msi2 in mammalian cortical development, hypothesizing that Msi2 transiently represses translation of key mRNAs to facilitate asymmetric NPC division. Using immunofluorescence and Western blotting, we have confirmed the presence of Msi2 within the CD1 mouse cortex throughout neurogenesis. In vitro shRNA knockdown experiments show that loss of Msi2 during early neurogenesis leads to an increase in NPCs and a proportional decrease in neurons in primary culture, suggesting that Msi2 is indeed a key component of ACD. Future research will examine putative Msi2 target RNAs using RNA-IP and RNA sequencing to confirm RNA binding, and dual-luciferase assays to provide evidence of translational repression. Taken together, these experiments suggest a role for Msi2 in ACD of NPCs, and improve our understanding of the formation of the mammalian cortex.

3-A-3 Investigating the functional role of RNA-binding protein hnRNP-Q, in regulating asymmetric cell divisions of neural precursor cells during cortical development

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The development of the cerebral cortex is a complex process reliant upon the collaborative efforts of a wide variety of molecular mechanisms, one of which is the ability of neural precursor cells (NPCs) to divide asymmetrically. Initiation of the neurogenic period marks the transition from proliferative self-renewing divisions to the asymmetric cell divisions of NPCs. As a result of these asymmetric cell divisions, both a precursor cell and a neuron is produced, each containing unequal distributions of cellular components. This discrepancy is created through the intracellular partitioning of components to selective sites that, in the case of proteins, utilizes mRNA localization as the means to do so. Heterogeneous nuclear ribonucleoproteins (hnRNPs) are a family of RNA-binding proteins that have been shown to aid in the localization of the transcripts they bind. Of particular interest is hnRNP-Q, known to localize specific mRNAs in Drosophila and which is found in ribonucleoparticles of neuronal dendrites. Based on this knowledge, we hypothesize hnRNP-Q to be involved in regulating asymmetric divisions of NPCs. The expression profile of hnRNP-Q reveals its presence throughout all stages of embryonic brain development and it appears to be distributed throughout the entire cortex. Moreover, in vitro knockdown experiments revealed altered patterns of precursor cell differentiation and self-renewal. Insight into the potential mechanism of these findings will come from future experiments that aim to co-immunoprecipitate the protein and mRNA binding partners of hnRNP-Q.

3-A-4 The Impact of Early-Adolescent Adversity on Social Behaviour and Serotonergic Innervation in Adulthood

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Stress causes changes to neurochemical systems and has a strong association with increased activation of the serotonin (5-HT) system. During adolescence, the brain undergoes vast and rapid changes and is thus vulnerable to disruption from adversity. Maladaptive social behaviours and threat-related responses are linked to changes in the 5-HT system. One potential mechanism for this change is an increase in 5-HT fiber density. Previous work found increased 5-HT levels in the ventral hippocampus of

adult male rats following prior exposure to adolescent stress. Use of the social interaction test allows for the assessment of social contact, investigation, and play-fighting behaviours in female subjects. Female Long-Evans rats were stressed with intermittent physical stress (IPS; consisting of water immersion, elevated platform, and foot shock) over the early adolescent period (postnatal day 22-34). Behavioural testing began on PD 61 and consisted of the elevated plus-maze (EPM), shock-probe burying (SPBT), and social interaction (SI) tests. In comparison to no-stress controls, rats in the early-adolescent stress condition showed increased open-arm activity in the EPM and decreases in playfighting behaviour in the SI test. Brain tissue was processed using immunohistochemistry and quantified using stereological probes to analyze 5-HT fiber density between groups in the prefrontal cortex, dorsal hippocampus, and ventral hippocampus. This work will provide a greater understanding of the mechanisms behind how early-adolescent stress impacts the 5-HT system into adulthood.

3-A-5 TRPM7 regulates axonal outgrowth and maturation of primary hippocampal neurons.

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Background: TRPM7, a calcium-permeable, ubiquitously expressed cation channel was shown to play a role in several processes such as cell adhesion, cytoskeletal regulation and migration. As these processes are necessary for neurite elongation, we investigated the role of TRPM7 in neuronal outgrowth in culture. Methods: Primary hippocampal culture, whole-cell patch-clamp, immunocytchemistry in conjunction with confocal microscopy, live-cell calcium imaging, western blotting and mass spectrometry were utilized in this study. Results: We found that siRNA knockdown and pharmacological inhibition of TRPM7 with specific blocker waixenicin A preferentially enhanced axonal outgrowth in a dose-dependent and calcium-dependent manner at several time points in culture. We found that TRPM7 interacts and colocalizes with two cytoskeletal proteins, F-actin and α-actinin-1. Based on these data, we propose a TRPM7-mediated mechanism of actin-based growth cone protrusion and neurite elongation. Conclusions: Neurite outgrowth is mediated at least in part through calcium-dependent TRPM7 mediation of cytoskeleton at the growth cone, making TRPM7 a potential therapeutic target for neurodegeneration.

3-A-6 Re-defining the niche of neural stem cells: determining new roles for forebrain interneuron-secreted signals in cortical progenitor cell oligodendrogenesis

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Oligodendrogenesis in the cortex occurs in two waves, with the first wave of oligodendrocytes generated by ventral forebrain neural precursors (NPCs), and the second by cortical NPCs. During this second wave, cortical NPCs are exposed to an environment that includes cortical neurons, interneurons that migrate through the precursor zones to populate the cortex, and ventrally-derived oligodendrocytes. We hypothesized that medial ganglionic eminence (MGE) interneurons that migrate through the VZ/SVZ of the embryonic cortex secrete factors that influence the biology of cortical NPCs. Culturing MGE neurons or conditioned media from these neurons with cortical NPCs increased NPC proliferation and oligodendrogenesis but not astrogenesis. Using ligand transcriptome data from MGE neurons and receptor transcriptome data from cortical NPCs, we modeled the MGE-neuron/cortical NPC niche, and predicted several paracrine interactions between MGE neurons and cortical NPCs. We

focused on the cytokine fractalkine (CX3CL1), and found that the oligodendrogenic effect of MGE neuron-conditioned media on cortical NPCs was inhibited by CX3CL1 or fractalkine receptor (CX3CR1) function-blocking antibodies. Knockdown of CX3CR1 in cortical precursors in vivo led to decreased formation of oligodendrocyte progenitors. Finally, in utero injection of CX3CL1 into the lateral ventricle of the developing brain increased the proportion of Olig2+ cells in MGE. We propose a novel developmental mechanism whereby migrating MGE interneurons secrete fractalkine and in so doing promote cortical oligodendrogenesis.

3-A-7 Loss of CREB alters brain anatomy

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CREB-dependent gene expression is activated by several signaling cascades and implicated in many complex processes, such as cell growth/survival and synaptic plasticity. Mutations of genes in the CREB signaling pathway are associated with neurodevelopmental disorders, including many "Rasopathies". Here we used whole-brain MRI to determine how congenital loss of CREB affects mouse brain anatomy and whether these effects depend on CREB dosage. Adult CREB αδ mutant mice (CREB+/+, CREB+/- and CREB-/-) were perfusion-fixed and imaged with ex-vivo MRI. Automated algorithms were used to align the images and compute the volumes of 62 structures in each brain. ANOVAs were performed to determine the effect of genotype on each structure/voxel volume. Gene dosage effects were modeled by treating genotype as an ordered factor and testing for linear vs. quadratic genotype effects. The cerebral cortex, many subcortical structures, and white matter tracts were significantly smaller in CREB-/- vs CREB+/+ mice, even after normalizing for brain volume. This suggests these areas either fail to develop fully or undergo degeneration. CREB+/- mice were phenotypically similar to CREB+/+ mice. The exceptions included white matter tracts, suggesting they may be more sensitive to disruption of CREB-dependent transcription. Intriguingly, there was a gene dose effect on cerebellar volume: volume increased with decreasing CREB dosage. Overall, disrupting CREB has widespread effects on neuroanatomy which may underlie the intellectual impairments seen in related neurodevelopmental disorders.

3-A-8 Examination of microRNAs in response to retinoic acid during growth cone guidance

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Prior to the formation of a synapse, neuronal growth cones guide extending axons towards their synaptic target with extreme efficiency and accuracy. The growth cone rapidly responds to various environmental cues, including classical chemotactic proteins such as netrins and semaphorins. Studies have also identified a variety of non-traditional guidance cues, including the Vitamin A metabolite, retinoic acid (RA). However, little is known of the underlying molecular mechanisms involved in growth cone turning in response to a RA gradient. MicroRNAs, a class of small, non-coding RNA transcripts, have emerged as potential candidates that contribute to growth cone guidance. Current studies have begun to explore the role of these non-coding RNAs in regulating gene expression and local protein synthesis underlying growth cone responses to traditional guidance cues. Our goal is to identify miRNAs that regulate growth cone guidance in response to RA. We have previously established that invertebrate growth cones exhibit positive turning towards RA in a local protein synthesis-dependent manner. We

now have evidence for the presence of miR-124 in these growth cones and axons, and are currently examining whether miRNAs are involved in the chemoattractive response to RA. These studies will advance our knowledge of growth cone dynamics, especially the underlying mechanisms of retinoic acid-induced chemoattraction, and further elucidate the role of miRNAs in the developing nervous system.

3-A-9 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 essential for circuitry assembly, and alterations in neuronal subtypes likely contribute to human cognitive disorders. However, the mechanisms regulating the genesis of distinct neuronal subtypes from neural precursor cells (NPCs) are still not understood. Here, we have addressed these mechanisms, focusing on the identity gene Brn1, which specifies superficial layer neurons, and show that translational regulation of this gene in NPCs controls the temporal generation of layer-specific neurons in the developing mouse cortex. Specifically, we found that while the Brn1 mRNA is transcribed in NPCs at early developmental timepoints when only deep layer neurons are specified, it is not translated until later timepoints coincident with the genesis of superficial layer neurons. At the earlier timepoints, brn1 mRNA is translationally repressed by the 4E-T repression complex. Disruption of this complex leads to early Brn1 protein expression and aberrant genesis of superficial layer neurons. To characterize this complex, we analyzed RBP-recognition motifs that are enriched in 4E-T-bound mRNAs, and identified Pum2 as a potential RBP in the complex, which interacted and co-localized with 4E-T in NPCs. Together, these results suggest that NPCs are transcriptionally primed so that they have the potential to generate diverse neuronal subtypes, but that 4E-T complex-mediated translational repression of identity mRNAs ultimately determines the appropriate timing and identity of their daughter neurons.

3-A-10 Early white matter development and outcomes in children born very preterm

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Objectives: To investigate white matter development in children born very preterm (VPT) and its relation to outcomes. Methods: 161 diffusion images were acquired in children born VPT (<32 weeks gestational age; median: 29 weeks). Each child was scanned within two weeks of birth, with up to three more scans at term-equivalent, two and four years of age. Diffusion tensors were computed to obtain measures of fractional anisotropy (FA), mean, axial and radial diffusivity. An FA template was created for each time point. A paediatric atlas was applied to obtain average diffusion metrics within twelve white matter tracts. Linear mixed effects models were performed to examine developmental trends and partial least squares analyses (PLS) were performed to explore associations between white matter growth and outcomes. Results: Age-related changes across time were present for the majority of tracts with decreased change between two and four years of age within the left posterior limb of the internal capsule, external capsule, posterior thalamic radiation, superior longitudinal fasciculus and superior frontal occipital fasciculus. Between preterm and term-equivalent scans, rates of FA change differed in

anterior versus posterior tracts. PLS analyses revealed associations between slower rates of AD and RD change within the external and internal capsule in the preterm period with lower IQ and language scores. Conclusion: These results characterize early white matter development and early biomarkers of functional impairments important for predicting outcomes of children born VPT.

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

3-B-11 Amyloid beta modulates excitotoxic currents during hypoxia.

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Ischemic stroke occurs when blood flow is reduced in the brain, resulting in downstream hypoxia and cell death. Under low oxygen conditions, there is excessive neurotransmission and impaired reuptake to astrocytes due to a loss of energy substrates (O2 and ATP). This results in excess glutamate receptor stimulation, anoxic depolarizations (aDPs) and excitotoxicity. The aDP is well characterized, and pannexin-1 channels (Panx1) have been demonstrated to be an important contributing factor to the aDP. Stroke survivors are at risk of neurodegenerative disorders such as Alzheimer's disease (AD), and it has been reported that brain hypoxia leads to increased production of the pathological form of the protein amyloid beta (Aβ). Aβ is aggregated into plaques in patients with AD, and oligomeric Aβ is thought to disrupt synaptic activity and contribute to the common symptoms of AD. Interestingly, little is known about the physiological role of Aβ, and of the reason behind its increased production during hypoxia. Our overall hypothesis is that physiological concentrations of Aβ can modulate responses to hypoxia. Using whole-cell patch clamp electrophysiology in rat pyramidal neurons of the CA1 region, the aDP was initiated using low oxygen (~5 mmHg). We show that low (pM-nM) concentrations of exogenous, soluble Aβ significantly attenuate the aDP. Aβ also attenuated secondary currents activated during excitotoxic NMDA exposure. Together, these data suggest a functional interaction of Aβ with Panx1 and that Aβ may have a protective role during hypoxia by limiting excitotoxicity.

3-B-12 Microglia analysis in T cell deficient mice

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The influence of the innate and adaptive immune system on mental health is an important topic for today's neuroscientists. Using T cell deficient mice, our group has shown that T cells contribute to anxiety-like behaviour. Ex vivo structural MRI showed brain volume differences in regions including the amygdala, bed nucleus of the stria terminalis (BST), dorsal raphe (DR), hypothalamus, hippocampus, and periaqueductal grey in immunocompromised mice. In several regions, there was a significant sex by genotype interaction suggesting that T cell-brain signaling may contribute to sex differences in neuroanatomy. Here, microglia were examined in adult mice lacking the beta and delta chains of the T cell receptor TCR(β-/-δ-/-) and wild type (WT-C57Bl/6) mice using immunohistochemistry with microglial marker Iba1. Microglia count was assessed through manual tracing of the soma perimeters using Axiovision 4.6. Previous works in rats has shown sex differences in microglia number and morphology in stress-related brain regions (Schwarz et al 2012 Neurochem 120:948; Lenz et al 2013 J Neurosci 33:2761). Our analysis to date reveals an increased number of microglia in the dorsal BST, but not ventral BST, in WT males compared to females, however this sex difference was not observed in TCRβ-/-

δ-/- mice. Interestingly, reduced numbers of microglia in the DR of TCRβ-/-δ-/- mice were observed compared to WT. Sex differences in microglial number were not observed in other brain regions examined. Ongoing analysis will determine possible differences in microglia activation state.

3-B-13 Unitary EPSCs at single primary afferent-lamina I neuron synapses show predominant role of GluN2B- and GluN2D-containing NMDA receptors

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NMDARs are expressed in the spinal dorsal horn where nociceptive information is integrated and relayed to the brain. Because NMDAR subtypes have distinct functional properties and have differing physiological/pathological roles, a major question has been the specific GluN2 subunit composition contributing to NMDAR function at a given synapse. To elucidate subtype at single synapses, we carried out voltage-clamp recordings of lamina I neurons in adult rat spinal cord slices and evoked unitary excitatory post-synaptic currents (uEPSCs; Vh: 60 mV) by stimulating a single afferent monosynaptic connection to the neuron recorded. uEPSCs exhibited consistent latency, amplitude, and clear stimulation threshold and were analyzed using decay time constant and charge transfer. Cluster analysis identified 3 groups ($p < 0.0005$) suggesting distinct NMDAR uEPSC kinetic properties at individual synapses. In one group (32%) the mean decay time constant of the uEPSC was fast (52 ms) and the charge transfer small (0.33 pC). A second subpopulation (15%) had a component with a long decay time constant (1192 ms) and large charge transfer (6.2 pC). The majority of synapses (53%) had a NMDAR component with an intermediate decay time constant (314 ms) and charge transfer (1.9 pC). GluN2B block (Ro25-6981) reduced intermediate decay uEPSCs while GluN2D block (DQP-1105) reduced long time decay uEPSCs. Lamina I glutamatergic synapses are therefore not uniformly identical but occur with deactivation kinetics consistent with that of GluN2A-, GluN2B-, or GluN2D-containing NMDARs, respectively.

3-B-14 Optogenetic Modulation of Septal Glutamatergic Neurons in the Freely Moving Mouse

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Neurons in the medial septum and diagonal band of Broca (MS-DBB) provide important connections to the hippocampus and are critical for spatial learning and memory. Three main neuronal populations have been identified in this region: cholinergic, GABAergic, and glutamatergic. It has previously been reported that glutamatergic neurons within the MS-DBB provide connections onto both GABAergic and cholinergic neurons, and also provide relatively sparse connections to the hippocampus. In addition, it has recently been shown that optogenetic activation of glutamatergic neurons can powerfully drive hippocampal theta rhythms, likely through intraseptal connections. While glutamatergic connectivity and strong influence on theta rhythms has been explored, their specific contribution to general behavior remains poorly understood. To further explore the role of MS-DBB glutamatergic neurons, we have used optogenetics to specifically target this neuron population. Using this model we aim to determine how modulation of glutamatergic neurons from the MS-DBB influence hippocampal rhythms and animal behavior. In the freely moving mouse, we have examined the effect of altering of this population on locomotion, exploration and memory. These experiments will help to understand how the role MS-DBB glutamatergic neurons play in freely behaving mice.

3-B-15 Effect of pirenzepine and muscarinic toxin-7 on muscarinic acetylcholine type-1 receptor internalization and downstream signaling cascades.

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Muscarinic receptors are a group of five G-protein coupled receptors (GPCRs) that are targeted as drugs for the treatment of several human pathophysiological conditions. Understanding the selectivity and specificity of muscarinic antagonists and their downstream GPCR associated signaling pathways are important for therapeutic exploitation. Pirenzepine (PZ) and muscarinic toxin-7 (MT7) are selective antagonists of the muscarinic acetylcholine type-1 receptor (M1R). Previously, we have shown that both PZ and MT7 induced neurite outgrowth in a dose dependent manner in cultured adult rodent dorsal root ganglion neurons. However, the exact mechanism of their effect on neurite outgrowth is unknown. In the present study, we compared the effect of PZ and MT7 on phosphorylation of M1R and subsequent arrestin-mediated internalization, multiprotein complex (MPC) formation and phosphorylation of extracellular signal-regulated kinase1/2 (Erk1/2) in vitro. Our findings indicate that M1R is significantly phosphorylated and internalized following treatment with PZ and MT7; however, the degree of internalization and association of M1R in different MPCs differed indicating a fundamental difference in downstream signaling cascades. Interestingly, we have found that MT7 can cause selective ubiquitination of M1R and significantly higher glycosylation of M1R when compared with PZ in vitro. Our results also showed that both MT7 and PZ significantly increased the phosphorylation of Erk1/2, however, the degree of ERK phosphorylation differed in a time dependent manner. Funded by CIHR # MOP-130282

3-B-16 Chronic ghrelin enhances long-term potentiation and memory in hippocampal CA2 region following streptozotocin-induced diabetes

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Hippocampal dysfunction may contribute to hyperglycemia related cognitive impairment in diabetes mellitus. Activation of ghrelin receptors in the hippocampus facilitates high frequency stimulation (HFS)-induced long-term potentiation (LTP) and also improves learning and memory. Here, it is reported that intraventricular ghrelin (200 ng/rat for 7 days) before and after the induction of diabetes by streptozotocin (STZ) prevented impairment of LTP and led to restitution of long-lasting potentiation of excitatory postsynaptic potentials (EPSPs) and population spikes (PSs) in CA2 area of anesthetized rats. Animals were intraperitoneally administered STZ (60 mg/kg) then received daily ghrelin injections into the brain ventricle. To assess cognitive performance, open-field and passive avoidance tests were performed. Intrahippocampal field potential recordings were done and immunohistochemistry to Bcl-2 and Bax was examined. The results demonstrated that ghrelin enhanced memory by significantly reducing step-through latencies in diabetic rats and also increased the EPSP slope and PS amplitude, suggesting the involvement of ghrelin in postsynaptic mechanisms of hippocampal LTP. The Bcl-2/Bax ratio is enhanced and the expression of Bcl-2 was sufficient to prevent apoptosis of hippocampal neurons. It was revealed that neuroprotective effects of chronic ghrelin not only can enhance but also can restore LTP in CA2 area of STZ-induced diabetic rats through inhibition of mitochondrial apoptosis. Therefore, exogenous ghrelin could have therapeutic value in cognitive deficits in diabetes.

3-B-17 L-type calcium channels functionally couple to IKCa channels to generate an IsAHP

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The slow afterhyperpolarization (sAHP) of CA1 hippocampal pyramidal cells was reported to involve intermediate calcium -activated potassium (IKCa) channels. Previous studies suggested that L-type channels represent a primary source of calcium to drive the sAHP. Recordings in tsA-201 cells confirmed a -10 mV difference in the voltage-dependence for Cav1.3 vs Cav1.2 channel activation in physiological levels of [Ca]o. Coexpressing IKCa channels with Cav1.2 or CaV1.3 channels in tsA-201 cells revealed voltage-dependent IKCa activation that closely followed that of CaV1 isoforms. Moreover, step commands of 5-150 ms evoked a graded IKCa tail current of 1-5 sec, as expected for IsAHP. An IsAHP could be recorded in CA1 pyramidal cells in blockers against all CaV channel isoforms except CaV1, with the IsAHP then abolished by TRAM-34, a selective IKCa blocker. The IsAHP was further reduced by perfusion of the DHP isradipine to block Cav1 currents. Cav1-mediated activation of IKCa in either cell type was blocked by 5 mM EGTA, suggesting a microdomain interaction. Immunolabel was detected for all of IKCa, CaV1.2, and CaV1.3 in CA1 cells but with no obvious co-localization. Together the results indicate a highly effective functional coupling between CaV1 and IKCa channels that promote a long duration activation of IKCa in the form of IsAHP. Funded by operating grants from CIHR (RWT).

3-B-18 p11 corticostriatal neurons have distinctive 5-HT responses sensitive to chronic social isolation stress and to antidepressant treatment

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Major depression affects more than 15% of North Americans in their lifetime. The most commonly prescribed antidepressant medications are selective serotonin reuptake inhibitors (SSRIs) that target the serotonin (5-HT) system. SSRI therapeutic action requires a prolonged period of treatment and is not always effective. To improve therapies for depression, it is essential to fine-tune the mechanisms of antidepressant action. Recently, layer 5a corticostriatal neurons expressing p11 (S100a10) protein were found to be specifically affected in depression and distinctively responsive to antidepressant treatment. Initially identified as an interacting partner for a group of 5-HT receptors, p11 expression is decreased in depression and increased by SSRIs. Yet, the critical mechanisms underlying the antidepressant neurophysiology of p11 remain to be elucidated. To characterize the distinctive neurophysiological properties of p11 expressing neurons, we performed whole cell electrophysiology on acute brain slices of motor cortex from mice with eGFP-labeled p11 expressing neurons. Here, we find p11 neurons have excitatory responses to 5-HT which are diminished in p11-null mice. Subjecting mice to chronic social isolation stress reduces 5-HT excitatory responses in p11 neurons but chronic treatment with the SSRI fluoxetine restores them. We probe the receptors and signaling mechanisms underlying the unique 5-HT responses of p11 neurons. Identification of these underlying regulatory mechanisms will be important for developing novel treatment strategies for depressive disorders.

3-B-19 ATP-binding Cassette Transporter A7 (ABCA7) Loss of Function Alters Alzheimer Amyloid Processing

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The ATP-binding Cassette Transporter A7 (ABCA7) has been identified as a susceptibility factor of late onset Alzheimer disease in genome-wide association studies. ABCA7 has been shown to mediate phagocytosis and affect membrane trafficking. The current study examined the impact of ABCA7 loss of function on amyloid precursor protein (APP) processing and generation of amyloid-ß (Aß). Suppression of endogenous ABCA7 in several different cell lines resulted in increased ß-secretase cleavage and elevated Aß. ABCA7 knock-out mice displayed an increased production of endogenous murine amyloid Aß42 species, which were detected by sandwich ELISA. Crossing ABCA7-deficient mice to an APP transgenic model resulted in significant increases in the soluble Aß as compared with mice expressing normal levels of ABCA7. Only modest changes in the amount of insoluble Aß and amyloid plaque densities were observed once the amyloid pathology was well developed, whereas Aß deposition was enhanced in younger animals. In vitro fluorescent imaging studies indicated a more rapid endocytosis of APP in ABCA7 knock-out cells that is mechanistically consistent with the increased Aß production. These in vitro and in vivo findings indicate a direct role of ABCA7 in amyloid processing that may be associated with its primary biological function to regulate endocytic pathways. A reduction in ABCA7 expression or loss of function would be predicted to increase amyloid production and that may be a contributing factor in the associated Alzheimer disease susceptibility.

3-B-20 An Evolutionary Switch in ND2 enables Src kinase regulation of NMDA receptors

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The non-receptor tyrosine kinase Src is a key signaling hub for upregulating the function of N-methyl D-aspartate receptors (NMDARs), which are critical for numerous physiological and pathological processes in the central nervous system (CNS). Anchoring of Src within the NMDAR complex is essential for the kinase to phosphorylate GluN2 subunits of the receptor and is dependent upon a mitochondrially encoded adaptor protein, NADH dehydrogenase subunit 2 (ND2). The interacting regions between Src and ND2 have been identified, but the interaction between ND2 and the NMDAR complex has remained elusive. Here, we generated a homology model of ND2 that was docked onto the NMDAR via the transmembrane domain (TMD) of GluN1. This interaction is enabled by the evolutionary loss of 3 N-terminal helices in bilaterian ND2 proteins compared to their ancestral homologs, which results in a deep groove to which M4 of GluN1 can bind. We experimentally validated our model of this complex by generating a series of NMDAR and ND2 mutants and performing colocalization and bimolecular fluorescence complementation analysis. Furthermore, we demonstrated that blocking this interaction with an ND2 fragment identified from our experimental studies prevents Src-mediated upregulation of NMDAR currents in neurons. Our findings are the first report of an NMDAR accessory protein that interacts with the TMD of one of the core subunits, and thus expands the repertoire of regulatory protein:protein interaction mechanisms within the NMDAR complex.

3-B-21 Role of Calpain in 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 cytosolic proteins (e.g. α-fodrin),

receptors (e.g. NMDAR) and scaffolding proteins (e.g. PSD-95), 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 proteins involved in synaptic transmission and plasticity. Given the importance of calpain and CaMKII in synaptic potentiation, we aimed to investigate if the two proteins act in different signalling pathways or if they are both part of the same pathway. In neuronal cultures, pharmacological inhibition of calpain activity blocked ERK phosphorylation and affected synaptic AMPA receptor content. This is in support of its role in NMDAR-dependent LTP. We then show, by immunolabelling and time-lapse imaging that CaMKII autophosphorylation and post-synaptic translocation is regulated by calpain activity. These results suggest a link between calpain and CaMKII signaling. Further experimentation will determine if calpain acts on CaMKII directly or indirectly. Our experiments might further our understanding of the molecular cascade supporting activity-dependent synaptic potentiation.

3-B-22 Investigating spiking resonance in computational models of oriens-lacunosum/moleculare (O-LM) hippocampal interneurons with dendritic synaptic inputs

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The theta rhythm (4-12Hz) is correlated with spatial navigation and mnemonic processing in the hippocampus. Inhibitory interneurons of the hippocampus fire action potentials at specific phases of the theta rhythm, pointing to distinct functional roles in shaping this rhythmic activity. Oriens/lacunosum moleculare (O-LM) interneurons regulate the activity of local pyramidal cells in CA1. They express the hyperpolarization-activated, mixed-cation current (Ih) and show spontaneous firing at theta that is impaired upon Ih block in vitro. A dynamic clamp study (Kispersky et al. 2012) showed that injecting theta frequency-modulated artificial synaptic inputs into the soma of O-LM cells resulted in theta spiking resonance that did not depend on the presence of Ih. Here, we used multi-compartment models of O-LM cells to examine the effect of dendritically-located synaptic inputs on spiking resonance. We selected models with dendritic Ih from our previous model database work and inserted Poisson-based excitatory and inhibitory synaptic inputs onto the dendritic tree. The input was modulated at various frequencies, including theta. We found that models expressed enhanced resonant firing at theta frequencies given dendritic synaptic inputs compared to somatic-only inputs. Thus, theta-timed inputs, such as from the medial septum, may preferentially target O-LM cell dendrites to maximally recruit firing at theta frequencies. Investigating these network interactions are of critical importance for understanding O-LM cell contributions to theta rhythm activity in the CA1 microcircuit.

3-B-23 The local and global influences of neuronal field effects in synchronized networks

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Communication between neurons is most often considered in a synaptic context, via chemical and electrical synapses. The ionic currents underlying action potentials give rise to electric fields, which can influence neurons at a distance independent of synaptic communication. This so-called "ephaptic coupling" is receiving more attention recently, but the consequences and mechanisms of action are not yet fully understood. We have developed a simplified modeling framework to study ephaptically-coupled networks that involves both ionic currents and the extracellular space. We found that for sufficiently dense networks, neurons act locally to facilitate spike generation, and increase frequency.

This synergy is associated with a net decrease in transmembrane current. As a result, the field effect per neuron at a distance is dramatically decreased. This implies that networks can grow in size without a correspondingly large increase in distant field effects (crosstalk), even during large-scale synchronous firing. In a computational context, this may serve as a form of gain control that limits the interaction between neighbouring networks through global field potentials.

3-B-24 The X-linked Intellectual Disability Gene, DHHC9, in Neurite Outgrowth and Synapse Formation

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The family of DHHC proteins, which encode palmitoyl acyltransferase (PAT) 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 both excitatory and inhibitory neurons where it plays an important role in promoting and maintaining dendritic outgrowth and arborisation, as well as modifying synapses. Our data suggests that this is palmitoylation dependent and is mediated through Ras GTPase. Together these results show that DHHC9 targets Ras to the plasma membrane where it plays an important role in regulating neuronal growth and synaptic density.

3-B-25 Complex molecular and functional outcomes of single versus sequential cytokine stimulation of microglia

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Microglia are the 'professional' phagocytes of the CNS. While phagocytosis is crucial for normal CNS development and maintenance, it can be both detrimental and beneficial after injury or disease. Microglia can acquire pro-inflammatory (M1) or anti-inflammatory (M2) activation states, which can affect cell functions, as well as ion channels that are potential targets for regulating their behaviour. Although microglia are exposed to a changing cytokine environment after injury or CNS diseases, little is known about molecular or functional consequences. Therefore, we applied several microglial activation paradigms (with or without myelin debris) to primary rat microglia: M1 (IFN-gamma+TNF-alpha; 'I+T'), M2a (IL-4), M1 to M2a, M2a to M1. We assessed: (i) gene expression reflecting their activation and inflammatory state, receptors and enzymes related to phagocytosis and ROS production, ion channels; (ii) myelin phagocytosis, production of reactive oxygen species (ROS), and contributions of several ion channels. We found that M1 stimulation increased pro-inflammatory genes, phagocytosis, ROS, as well as expression of KCa3.1, Kv1.3 and Kir2.1 channels. M2a increased anti-inflammatory genes, ROS production, and KCa3.1 and Kv1.3 channels. Myelin phagocytosis enhanced the M1 profile and dampened the M2a profile, and both phagocytosis and ROS production were dependent on NOX enzymes, Kir2.1 and CRAC channels. Importantly, microglia showed some capacity for re-polarization between M1 and M2a states, based on gene expression changes, myelin phagocytosis, and ROS production.

3-B-26 Radial Glial Motility Regulates Synaptic Development in the Visual System

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Radial glia (RG) are present from the earliest stages of central nervous system (CNS) development. They possess many fine, highly dynamic filopodial processes that undergo significant restructuring over minutes. We probed the signaling pathways regulating RG in the optic tectum of Xenopus laevis and investigated the function of this motility in circuit formation in vivo. RG were imaged by two-photon microscopy in the optic tectum of intact Xenopus laevis tadpoles (stage 48). We found that neuronal NMDAR activity promoted glial filopodial motility through the activation of glial cGMP-dependent protein kinase 1 (PKG1) downstream of guanylyl cyclase. PKG1 is an upstream modulator of Rho family small GTPases that control actin cytoskeletal dynamics. To examine the function of RG filopodia motility in circuit development, we expressed either a dominant negative PKG1, constitutively active RhoA(Q63L), or dominant negative Rac1(N17) during a period of extensive synaptogenesis in the retinotectal system. We assessed synaptic connectivity by recording miniature excitatory postsynaptic currents (mEPSCs) from tectal neurons. Inhibiting PKG or Rac signaling in RG greatly decreased their rates of filopodial motility; neighboring neurons formed fewer mature synapses as revealed by a decreased mEPSC frequency. RhoA(Q63L) overexpression, which caused the glial filopodia to retract almost entirely, lowered both mEPSC frequency and mean amplitude. In conclusion, RG fine filopodial motility is regulated by PKG1 signaling and is crucial for normal excitatory synapse development in the CNS.

3-B-27 Theta-frequency stimulation of the parasubiculum promotes short- and long-lasting changes in entorhinal cortex responses to sensory cortical input

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The entorhinal cortex receives sensory input from the piriform cortex, and in turn projects to the hippocampus. The entorhinal cortex also receives the major output of the parasubiculum, allowing the parasubiculum to influence entorhinal cortex responses to sensory input. Neural activity throughout the hippocampal formation is heavily modulated by rhythmic oscillations at theta frequency. The current study assessed how rhythmic stimulation of the parasubiculum affects entorhinal cortex responses to sensory input, in order to demonstrate the role of the parasubiculum in modulating sensory input to the hippocampal formation. Whole-cell patch clamp recordings of layer II medial entorhinal cortex neurons were obtained. Trains of stimulation at theta frequency were delivered to the parasubiculum, followed by single pulses of stimulation to layer I of the entorhinal cortex at differing intervals. Results showed that parasubicular stimulation either suppressed or enhanced entorhinal cortex responses to layer I stimulation depending on the interval, with these effects mediated by GABAA receptors and the cationic channel Ih, respectively. Repeated low-frequency pairings of parasubicular theta trains and layer I stimulation pulses resulted in a lasting depression of entorhinal cortex responses to layer I input. These results demonstrate the ability of the parasubiculum to cause both short-term and lasting alterations in how the entorhinal cortex responds to sensory input, suggesting a role for this structure in determining the salience of sensory inputs to the hippocampal formation.

3-B-28 Extracellular Turrets in Domain II and Domain IV as Critical Determinants of Ion Selectivity in LCav3, the T-type Calcium Channel from Lymnaea stagnalis

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Our research is in evaluating the structural determinants for Ca2+ and Na+ selectivity in Cav3 T-type calcium channels. T-type channels can have ion selectivity that resembles voltage-gated calcium channels, but many invertebrates also have splice isoforms which are Na+ selective. The extracellular (S5P) turret, upstream of the selectivity filter in Domain II, is critically important for generating highly Na+ selective T-type channels. Native splicing of exon 12a generates a highly Na+ selective T-type channel. Exon 12b, on the other hand, generates a more Ca2+ selective T-type channel. We have swapped Domain II turrets between a Na+ selective invertebrate T-type channel from Lymnaea stagnalis (LCav3-12a) and a Ca2+ selective, mammalian Cav3.2 channel. Another region contributing to ion selectivity is the extracellular turret of Domain IV. Like Domain II, the Domain IV turrets are different between Na+ and Ca2+ selective channels, mainly in size and arrangement of cysteine residues. Selectivity was altered by swapping Domain II and Domain IV turrets from a Cav3.2 channel into an LCav3 T-type channel. Before the turret swap, the LCav3 T-type channel exhibits Na+ selectivity reminiscent of Nav1 channels. After the swap, the chimeric T-type channel exhibits selectivity that is more like the Ca2+ selective Cav3.2 channel. We are attempting to resolve the molecular mechanisms involved in generating dramatic ion selectivity changes in invertebrates. Domain II and IV extracellular turret sequences are implicated as critical determinants of ion selectivity in T-type channels.

3-B-29 Modulation of a non-selective cation channel by PIP2 and its metabolites controls excitability in Aplysia bag cell neurons

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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 Ca2+-dependent, protein kinase C (PKC)-activated, voltage-gated, non-selective cation channel, that exhibits characteristics consistent with transient receptor potential (TRP) channels, provides the depolarizing drive to maintain the afterdischarge. During the afterdischarge, phospholipase C (PLC) is activated, hydrolyzing phosphatidylinositol 4,5-bisphosphate (PIP2) into diacylglycerol (DAG), a potent PKC activator, and inositol triphosphate (IP3), a mobilizer of internal Ca2+. We investigated the interaction between the cation channel, PIP2 and its metabolites. The cation channel desensitizes following prolonged exposure to high Ca2+ at the cytoplasmic face of the channel in excised, inside-out patches. In an analogous manner, and similar to TRPC channels, DAG transiently increases the activity of the channel, followed by a decrease in activity below the initial level. In addition, under whole-cell voltage-clamp, we find that DAG activates a large, transient inward current through a disparate, voltage-independent cation channel, and this effect is amplified in the presence of IP3. Regulation of cation channel activity by PIP2 may include channel inhibition through lipid-protein interactions that is abolished upon hydrolysis by PLC, sparking channel modulation by DAG and/or IP3 to ultimately result in temporal control of cation channel activity and afterdischarge duration.

3-B-30 The Application of FTIR Spectroscopy to Image Metabolic Alterations Associated with the Glial Response Following Brain Ischemia

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Stroke is the leading cause of disability and the 3rd leading cause of death to Canadians. Although much is known about the metabolic alterations that occur during and following brain ischemia, effectively imaging the distribution of these alterations is rarely achieved. Consequently, much remains unknown about the physiological consequences of many ischemic induced biochemical alterations. A specific example is the accumulation of glycogen in astrocytes following an ischemic insult. It is well established that glial proliferation occurs after an ischemic insult. Individual glial cells also increase the abundance of glucose transporters on their end-feet processes, which increases their glycogen storage capabilities. It is also known that a mild ischemic preconditioning event can be neuroprotective against a subsequent larger ischemic insult. However, due to the inability to effectively image glycogen and important metabolic end products, particularly lactate, the role of astrocyte glycogen accumulation in any afforded neuro-protection remains elusive. By using Fourier Transform Infrared (FTIR) spectroscopic imaging, alongside conventional histochemical detection of glycogen and glial cells, we have shown that astrocytes accumulate glycogen following photothrombotic stroke in the mouse. This study demonstrates that FTIR imaging has immense potential to be used in this field to image the relative distribution of glycogen and lactate. Manipulation of glial cell energy storage capacity and metabolism could play an important role in future therapeutic interventions.

3-B-31 Two-photon imaging of GABAA receptor-mediated antidromic discharge in primary somatosensory neurons

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Primary afferent depolarization (PAD) results from activation of GABAA receptors on the central terminals of primary somatosensory afferent neurons. Due to their high intracellular chloride concentration, central terminal GABAA receptor activation causes membrane depolarization but also inhibition of spike initiation as a result of shunting effects and sodium channel inactivation. However, PAD may evoke spikes that can then propagate antidromically to cause neurogenic inflammation. We have shown in somatic recordings that PAD-evoked spiking requires both a depolarizing shift in EGABA and changes in voltage-gated ion channels that result in increased neuronal excitability. This combination of effects can arise in damaged peripheral nerves via enhanced function of the Na-K-Cl cotransporter, NKCC1, and downregulation of Kv1-type potassium channels, respectively. However, it remains unclear if these requirements are met in central axon terminals. Therefore, we have used two-photon imaging at the dorsal root ganglion (DRG) to image the antidromically propagating spikes evoked by GABA applied to axon terminals in the spinal dorsal horn. Using a novel spinal cord-DRG preparation with Cre-dependent GCaMP6f transgenic mice, action potential evoked calcium transients were detected at the DRG with high spatial and temporal resolution. It was found that only when NKCC1 activity is enhanced and Kv1-type channels are blocked could GABA initiate antidromically propagating action potentials from the central terminals.

3-B-32 Mechanisms of cocaine-induced increases in mu opioid receptor expression in PC12 cells

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Cocaine use has been linked to increases in mu opioid receptors (MOR) at the protein and mRNA level in key regions of the brain involved in motivated behaviours. This particular neuro-adaptation plays a

critical role in cocaine addiction and vulnerability to relapse. Furthermore, cocaine is a known inhibitor of the dopamine transporter (DAT) and this inhibition has been strongly linked to its addictive properties. Hence, the objective of this study is to identify possible mechanisms through which cocaine regulates the expression of the MOR. It is hypothesized that the cocaine-mediated expression of the MOR occurs via inhibition of the DAT. To test this hypothesis, PC12 cells were treated with three concentrations (0.1μM, 1μM, and 10μM) of GBR 12909, a potent DAT inhibitor. Treatments followed a repeated intermittent treatment (RIT) protocol, in which cells were exposed to their respective treatment condition three times per day for 30 minutes each. RNA was harvested from the cells 48 hours after treatment, reverse transcribed, and qPCR was used to quantify the relative expression of MOR mRNA in the respective treatment groups. RIT with 100 uM cocaine significantly increased MOR mRNA levels and this change in expression is being compared to mRNA levels in GBR12909-treated cells. These studies will provide novel evidence for opioid-dopaminergic interactions at the cellular levels and may identify potential new targets for effective pharmaceutical therapies of cocaine addiction.

3-B-33 Serotonin and mechanisms of cortical gain control: A novel synergy between 5-HT1A and 5-HT2A receptors in layer 6 pyramidal neurons of prefrontal cortex

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There is emerging evidence for the role of cerebral cortex layer (L)6 pyramidal neurons in cortical gain control. As such, the modulation of prefrontal L6 neurons may have important consequences for executive function. Here, we show that serotonin robustly inhibits prefrontal layer 6 neuronal excitability. This serotonergic inhibition is mediated through the combined direct effects of 5-HT1A and 5-HT2A receptors. To probe the consequences for mechanisms of L6 cortical gain control, we used transgenic mice in which L6 pyramidal neurons can be optogenetically-activated. We find that prefrontal L6 pyramidal neurons strongly excite L5 GABAergic interneurons. Furthermore, this cross-lamina excitatory connection between L6 pyramidal neurons and L5 GABAergic interneurons is strongly suppressed by serotonin. Antagonists of both 5-HT1A and 5-HT2A receptors are required to completely block this suppression. Together, these findings suggest a novel modulatory mechanism for serotonin to alter the signal-to-noise ratio within circuits important to executive function.

3-B-34 Investigating the transcriptomic basis of brain-wide electrophysiological diversity

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Brains achieve efficient function through implementing a division of labor, in which different neurons serve distinct computational roles. Neuronal computations are established through the expression of combinations of ion channels and associated proteins which define neuronal electrophysiological properties. Despite numerous studies characterizing neuronal physiological properties and gene expression patterns, linking neuron transcriptomics to function has been challenging due to the complexity of these heterogeneous data. Here, employing neuroinformatics approaches, we combine published reports of neuronal physiological properties with public transcriptomic datasets. Specifically, we integrate NeuroElectro, a database of literature-mined neuron-type physiological diversity, with NeuroExpresso, a database of microarray-based gene expression profiles from purified brain cell-types. This approach allows us to assess how electrophysiological differences among neuron types throughout the brain arise through their underlying patterns of gene expression. We find that there are many genes

whose expression levels are highly correlated with brain-wide electrophysiological diversity, including Hcn3 for resting potential and Cacna1a for action potential width. This correlative analysis also identifies numerous other genes not obviously related to neuronal electrophysiology, including ion transporters, synaptic proteins, and transcription factors. While these correlations may not reflect truly causative relationships, they represent novel hypotheses that can be tested experimentally.

3-B-35 The effect of selective 5-HT2A receptor agonists on the BDNF, GDNF and CDNF genes expression in the mouse brain

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Serotonin 5-HT2A receptors play an important role in the mechanisms of antidepressant and antipsychotic drug action. On the other hand neurotrophic factors, such as BDNF, GDNF and CDNF also involved in the pathology or treatment of many psychiatric diseases. However, the role of 5-HT2A receptors in the regulation of BDNF mRNA levels in vivo was not examined using highly selective agonists, whereas influence of 5-HT2A receptors on GDNF and CDNF genes expression in vivo was not studied at all. The effect of 5-HT2A receptor chronic activation with mixed 5-HT2A/2C receptor agonist DOI, selective agonists TCB-2 and 2C-CN-NBOH (60 and 100 times more selective than DOI respectively) and saline on the BDNF, GDNF and CDNF mRNA levels were investigated. We found that DOI decreased GDNF mRNA expression in the substantia nigra (SN), but failed to produce any effects on BDNF and CDNF mRNA levels. TCB-2 and 2C-CN-NBOH significantly increased BDNF mRNA expression in the hippocampus (HP), SN and striatum in selectivity dependent manner. TCB-2 decreased GDNF as well as CDNF mRNA levels in the frontal cortex (FC) and the GDNF mRNA level in raphe nuclei area of midbrain. 2C-CN-NBOH increased both GDNF and CDNF mRNA expression in the HP, but decreased CDNF mRNA expression in the SN. Thus, for the first time the effect of 5-HT2A receptor chronic activation on the BDNF, GDNF and CDNF genes expression in vivo was shown. The study was supported by the Russian Scientific Foundation (#14-25-00038).

3-B-36 NMDAR co-agonist D-serine promotes synapse maturation and stabilization of axonal branches in the developing visual system

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N-methyl-D-aspartate receptor (NMDAR) activation is essential for establishing and maintaining precise neural circuit refinement. The gliotransmitter D-serine is a co-agonist for NMDARs and modulates synaptic transmission and plasticity mediated by this receptor. Here we investigated the role D-serine plays in modulating synaptic transmission and axonal remodeling in the developing visual system of the Xenopus tadpole. We find that D-serine is an endogenous co-agonist of the NMDAR that is normally present below saturating levels. Using enzymatic biosensors we find that D-serine release in the optic tectum can be driven by glutamatergic activation and find that facilitating NMDAR activation by chronically elevating levels of D-serine promotes the maturation of functional synapses. Conversely, decreasing levels of endogenous D-serine reduces NMDAR-mediated synaptic transmission and results in deficits in synaptic maturation. To examine the effects of D-serine on retinotectal axonal development, in vivo 2-photon images of single-transfected GFP-expressing retinal ganglion cell axons were collected daily over 4 days to assess growth and branch elaboration, and at shorter (10 min) intervals to assess branch dynamics. We find that increasing available D-serine results in the

hyperstabilization of retinal axon branches. Axonal arbors become less complex compared to control axons over 4 days of treatment with D-serine. Together, these findings reveal an important role for D-serine in promoting NMDAR-mediated synaptic maturation and stabilization of axonal branches.

3-B-37 Hypoxic glioblastoma cells utilize a specialized protein synthesis machinery to synthesize PB-cadherin during migration and invasion

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Despite the diversity found in the mutational profile of brain tumors, they share the same physiological attributes known as the tumor microenvironment. Hypoxia, an aspect of the tumor microenvironment, initiates a selective mRNA translation program mediated by the cap-binding protein Eukaryotic Translation Initiation Factor 4E Family Member 2 (eIF4E2) to synthesize hypoxia-response proteins. Pituitary and brain cadherin (PB-cadherin), a calcium-dependent cell-cell adhesion molecule and direct mRNA target of eIF4E2, plays a role in mammalian neurogenesis. Recently, it has been associated with an aggressive cancer phenotype. However, the functional significance of PB-cadherin in glioblastoma multiforme (GBM) has not been investigated. Here, we show that eIF4E2 drives the synthesis of PB-cadherin and other hypoxia-response mRNAs. Silencing eIF4E2 in U87-MG cells resulted in decreased migration and invasion under hypoxia. Our future goals are to block PB-cadherin with a neutralizing antibody or silence PB-cadherin in the U87-MG cell line to determine its effects on hypoxic migration and invasion. Together, our results show the functional significance of eIF4E2 in GBM and may provide evidence for a novel role of PB-cadherin in promoting the invasion and metastasis of GBM under hypoxia. Our data suggest that eIF4E2 may serve as a potential drug target in future GBM therapies.

3-B-38 Learning Regulates the mRNA Demethylase FTO and mRNA Methylation

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Translation of mRNA into proteins is vital for memory formation, as evidenced by local, spine-specific mRNA translation occurring in response to synaptic stimulation and the inhibition of memory expression produced by the administration of translational inhibitors. Although the role of translation in memory is well accepted, the actual mechanism that underlies local control of translation is poorly understood. In this study, we explored whether mRNA methylation is involved in regulating learning-induced translational control, providing a first test of this novel mechanism in learning and memory. RNA can be heavily modified, with the most abundant modification being the methylation of adenine. Recent advances have begun to elucidate the potential roles of mRNA methylation with its most promising role being the potential to control mRNA translation. The ability to locally control translation via mRNA methylation makes this modification particularly enticing for regulating synaptic activity, where local control of translation in synapses is vital for synaptic plasticity. Here, we provide the first direct exploration of the role of mRNA methylation and the mRNA demethylase Fto in cognition. Using contextual fear conditioning in mice, we demonstrate that associative learning dynamically regulates Fto expression and mRNA methylation in area CA1 of the dorsal hippocampus. Additionally, it appears that only the synaptic fraction of FTO is reduced by training. These studies represent the first attempt to link epitranscriptomics, local regulation of translation, and memory.

3-B-39 GABAA receptors are novel targets for ketamine

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Introduction: Ketamine is widely believed to depress brain function by inhibiting the NMDA subtype of glutamate receptors. However, high concentrations of ketamine have been shown to increase the activity of a subtype of GABAA receptors (GABAARs) that contains α6 and δ subunits. These receptors are expressed almost exclusively in the cerebellum. It is unknown whether clinically relevant concentrations of ketamine modulate other GABAARs that are expressed in other brain areas. Here, we determined whether ketamine modifies the activity of native GABAARs in the hippocampus. Methods: Voltage clamp recordings were used to record whole-cell currents in cultured murine hippocampal neurons. DL-APV (20 μM) was added to block NMDA receptors. Results: Clinically relevant concentrations of ketamine (10-300 μM) increased GABA-evoked currents but only when receptors were activated by low concentrations of GABA (0.3-0.5 μM). Ketamine (10-1000 μM) potentiated a tonic GABA current in a concentration-dependent manner. Higher concentrations of ketamine (0.3-50 mM) alone directly activated GABAARs (EC50 = 6.4 mM). Interestingly, both the up-regulation and direct gating effects of ketamine were not affected by the α6-containing GABAAR antagonist furosemide (300 μM), or by genetic deletion of δ subunit-containing GABAARs. Conclusions: The ketamine effects are not restricted to α6 and δ subunit-containing GABAARs. Extrasynaptic GABAARs are preferentially sensitive to ketamine, and these receptors may contribute to the anesthetic, analgesic and anti-depressant properties of ketamine.

3-B-40 Intersectin1 is required for developmental enhancement of Ca2+-dependent replenishment of the readily-releasable synaptic vesicles

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Intersectin1 (Itsn1) is an evolutionally conserved scaffold protein engaged in clathrin-mediated endocytosis and a key molecular substrate for coupling exocytosis and endocytosis. However, it remains unknown if Itsn1 is required for development of synaptic functions in mammalian central synapses. To address this issue, we examined synaptic properties of the developing calyx of Held synapse in the auditory brainstem from wild-type (WT) and Itsn1 knockout (KO) mice at different postnatal (P) stages (immature P8-10 vs mature P16-20). Immunohistochemical analyses showed that Itsn1 proteins co-localized with a presynaptic marker vGlut1 in WT synapses for both age groups. By stimulating presynaptic axons, we found that deletion of Itsn1 had little effect on basal excitatory synaptic transmission or short-term depression (STD) as a result of depletion of synaptic vesicles (SVs) from the readily-releasable pool (RRP) in immature and mature synapses. In contrast, the fast Ca2+-dependent component of recovery from STD was selectively attenuated in mature Itsn1 KO synapses but remained unaltered in immature Itsn1 KO synapses. Surprisingly, blockade of the interactive partner of Itsn1, dynamin, with specific inhibitors did not slow down the recovery time course at the mature WT synapses. These results indicate that fast Ca2+-dependent replenishment of SVs in the RRP to the depleted sites is mediated by distinct mechanisms at different developmental stages, being strongly enhanced by Itsn1-dependent and dynamin-independent signaling during synapse maturation.

3-B-41 TLR4-mediated increase of microglial glycolysis inhibits expression of LTP through IL-1β

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The role of microglia and neuroinflammation in CNS function and neurodegenerative diseases has gained increasing support. It is therefore important to understand the mechanisms of microglial activation and explore ways to promote the resolution of inflammatory responses. Work in the peripheral immune system has demonstrated the role of cellular metabolism in regulation of immune cell polarization. Following activating stimuli, immune cells become highly glycolytic, while anti-inflammatory polarization is associated with enhanced oxidative phosphorylation. We have therefore investigated the role of metabolic pathways in microglial activation. Following LPS stimulation, microglial cultures showed a rapid increase in the production and secretion of the pro-inflammatory cytokine, IL-1β. Additionally, LPS activation impaired long term potentiation (LTP) in acute hippocampal field recordings. Interestingly, pre-treatment with the glycolytic inhibitor 2-deoxy-D-glucose (2DG) rescued LPS-induced IL-1β production and LTP impairment. We present evidence that LPS stimulates TLR4 on microglia to drive HIF-1α mediated IL-1β production, which inhibits neuronal LTP through IL-1R. To confirm a change in cellular metabolism, we are using Seahorse analysis of microglial cultures and fluorescence lifetime imaging of endogenous NADH in acute hippocampal slices. These results are exciting for the field of neuroinflammation, as they implicate cellular metabolism as a potential mediator of microglial activation, and suggest an inflammatory pathway that may lead to cognitive deficit.

3-B-43 Mu opioid receptor function in the anterior cingulate cortex

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Morphine isolated from the opium poppy has long been used as an effective pain killer. Its ability to induce analgesia mainly relies on the presence of the mu opioid G protein-coupled receptor (MOR) in pain pathways. Both endogenous and exogenous opioids that bind these receptors are able to modulate sensory information processing in the peripheral nerves, spinal cord and brain. Interestingly, MOR is expressed in the anterior cingulate cortex (ACC), a subdivision of the prefrontal cortex involved in the emotional and affective aspect of pain experience. Patients experiencing acute or chronic pain show a decrease in MOR availability in this brain region. The decrease in receptor availability is thought to be due to the action of endogenous opioid peptides causing MOR internalization, and recent studies suggest that pain relief is dependent on endogenous opioids in the ACC. It is currently unknown which neuronal cell types in the ACC express MOR. We use a functional approach based on patch clamp electrophysiology and pharmacology in mouse acute cortical slices as a powerful method to assess MOR expression at the cellular level in the ACC. Our preliminary data suggest that pyramidal cells in layer 2/3 express MORs as their firing activity is sensitive to the selective agonist DAMGO. We will proceed to investigate changes in MOR availability and DAMGO sensitivity in the ACC under normal versus neuropathic pain conditions. Supported by CIHR, LAEF.

3-B-44 The Role of the Tubulin-Cytoskeleton in the Modulation of the Connexin 36 Nexus

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Previous studies have demonstrated an equivalent to synaptic plasticity at connexin 36 (Cx36) electrical synapses. In the process of characterizing the molecular and cellular mechanism facilitating plasticity at

electrical synapses, we tested the hypothesis that the interaction of Cx36 with the tubulin-cytoskeleton is necessary to achieve plasticity at electrical synapses in neurons. To address this question the binding of Cx36 to tubulin was characterized in Neuro2a cells, using BioID, total internal reflection fluorescence (TIRF) and fluorescence recovery after photobleaching (FRAP) technology in living cells. In vitro, the binding was confirmed by GST-pull down assays and CoIP. Wild-type and mutant proteins, together with pharmacological blockers or TAT peptides were used to characterize further the interaction. The primary results of this study demonstrate that Cx36 interacts primarily with the β-tubulin isoform to regulate the trafficking and aggregation of connexons at the gap junction plaque (GJP). The amino acid Lys279 in the c-terminal binding (CTB) domain is critical for this interaction. During a simulation of plasticity in vitro, GJPs became more stable, an observation plausibly attributed to the interactions with the cytoskeleton and associating proteins. Finally, we demonstrate that plasticity is reversibly abolished in the presence of the tubulin-inhibitor colchicine. We conclude that cytoskeletal-dependent interaction with tubulin is required to modulate the strength of Cx36 synapses.

3-B-45 Dissecting the Role of Connexin 36 and Calmodulin in the Plasticity of Electrical Synapses

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Electrical synapses synchronize neural activity on millisecond timescales via cooperative interactions with chemical synapses and that this interaction contributes to mechanism for neuroplasticity. Our research focuses on the major electrical synaptic protein connexin 36 (Cx36), and the interaction with two calcium dependent proteins, calmodulin (CaM) and calmodulin kinase II (CaMKII). Previously, our group has described the run-up phenomenon involving the interaction of Cx36 and CaMKII as a physiological signature of plasticity at electrical synapses. On this basis, we have proposed that chemical and electrical synapses share, at least in part, a molecular machinery involving CaMKII and CaM to achieve plasticity. To resolve the role of CaM in the process, the interaction of Cx36 and CaM was investigated in living cells and using in vitro assays. Using FRET analysis and dye transfer, site directed mutagenesis, pharmacological blocking and a calcium binding deficient CaM, we demonstrated that at a cellular level binding of CaM to Cx36 is calcium dependent and already occurring before Cx36 enters gap junction plaques. Within a core CaM binding motif, amino acid W277 of the Cx36 protein is critical for binding in living cells. The key results obtained in living cells were further substantiated using isothermal titration calorimetry (ITC) and by resolving the structure using NMR. We conclude that the interaction between Cx36 and CaM plays a crucial priming role for subsequent activities of Cx36 and a key regulatory step in plasticity of electrical synapses.

3-B-46 Stable changes in H2A.Z incorporation and acetylation during memory formation and maintenance

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Memory formation is a protracted process that initially involves the hippocampus and becomes increasingly dependent on the cortex as the memory ages. Existing research has implicated stable changes in DNA methylation as a contributor to this process, whereas changes in histone modifications are typically found to be transient. Here, we investigated whether histone H2A.Z, a newly identified epigenetic regulator of learning and memory, is stably modified in the hippocampus and the cortex at

delayed time points after learning. To this end, mice were exposed to contextual fear conditioning and brains were collected either 24h or 30 days after training. Using chromatin immunoprecipitation, we quantified H2A.Z and acetylated H2A.Z (AcH2A.Z) binding on memory-related genes. 24h after training, we observed increased levels of H2A.Z acetylation on immediate early genes in fear conditioned mice in the hippocampus, whereas changes in total levels of H2A.Z binding on these genes were minimal. In contrast, 30 days after training, we observed an effect of training both on total levels of H2A.Z binding and on the levels of histone acetylation in the cortex, particularly on synapse-associated genes. We previously showed that H2A.Z in both the hippocampus and the cortex is transiently modified after learning. Here, we show that H2A.Z is stably regulated, but that this regulation is gene-specific, such that changes associated with immediate-early genes are no longer evident at 30 days, whereas changes associated with synaptic genes persist to support memory maintenance.

C – Disorders of the Nervous System

3-C-47 The Ontario Neurodegenerative Disease Research Initiative (ONDRI) Study: Using eye movements to identify cognitive and motor impairments in neurodegeneration

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Neurodegenerative diseases affect millions of aging individuals worldwide. The prevalence and care these individuals require is increasing dramatically. Identifying these conditions as early as possible is necessary for improving the efficacy of care. ONDRI is a longitudinal study to investigate neurodegeneration across patients diagnosed with Alzheimer's disease, mild cognitive impairment, Parkinson's disease, amyotrophic lateral sclerosis, frontotemporal dementia, or vascular cognitive impairment. Patients are recruited in multiple research centres across Ontario. The goal is to characterize predictors of neurodegeneration by providing deep endophenotyping that includes demographic, medical and neuropsychological tests, genetic analysis, MRI imaging, ocular tests, gait tests, and eye tracking. We describe the results of standardized video-based eye tracking that is performed on both clinical and control participants (50-90 years). Participants were seated in front of a computer and performed 240 trials of interleaved pro- and anti-saccade tasks. A coloured fixation point conveyed the instruction for a pro-saccade (look toward peripheral target) or anti-saccade (look away from peripheral target). We analyzed task errors, reaction times, accuracy, and metrics of the saccades, as well as pupil dynamics. There were age-related changes in performance and metrics among the control participants. In addition, all patient groups showed age-controlled abnormality on subsets of the dependent measures and the pattern of abnormality was unique for each patient group.

3-C-48 The role of the 'cholesteryl ester transfer protein' in Alzheimer's disease pathology

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Background: The cholesteryl ester transfer protein (CETP) is a plasma lipid transfer protein that exchanges cholesteryl esters from high-density lipoproteins (HDL) to low-density lipoproteins (LDL) and consequently promotes atherogenic lipoprotein ratios. High cholesterol levels are a well-established risk factor for Alzheimer's disease, the most common form of dementia. Importantly, genetic studies

associated CETP polymorphisms with a reduced risk of developing dementia. Hypothesis: We hypothesize that CETP activity is detrimental for the progression of Alzheimer's disease. Our objective is to determine the effect of CETP on amyloid precursor protein processing and Alzheimer's disease pathology using cell culture and mouse models. Methods: Levels of toxic amyloid-β peptides were measured using ELISA. The expression of Alzheimer's disease risk genes was determined by RT-qPCR. To measure the relative abundance of lipids in the brain, mass-spectrometry imaging was employed. Results: In cell culture, CETP activity increases the amount of secreted amyloid-β peptides. In CETP transgenic animals, inflammatory cytokines are up regulated, and Alzheimer's risk genes are modulated. Interestingly, CETP activity alters the brain lipid composition and distribution. Conclusion: We conclude that CETP activity may increase the risk for Alzheimer's disease through multiple pathways. First, CETP activity stimulates the generation of amyloid-β peptides. Further, in CETP transgenic animals, the brain lipid composition is altered and cholesterol-induced inflammation is stimulated.

3-C-49 Improved Phenotype in Adult Sandhoff Disease Mice Following Intravenous Administration of Self-complementary Adeno-associated Viral Vector Expressing a Novel Hexosaminidase Enzyme

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GM2 gangliosidosis stems from Hexosaminidase A (HexA) enzyme deficiency. In humans, HexA is the sole enzyme able to catabolize GM2 ganglioside (GM2); deficiencies can result in severe neurodegeneration and death. HexA is comprised of 2 subunits (α, β). Recently, Tropak et al. (Mol Ther Methods Clin Dev, in press), created a variant subunit, named μ, by combining the stabilization and catalytic properties of the human β- and α-subunits. The μ-subunit, coded by HEXM, forms a functional homodimer (HexM) able to hydrolyse GM2. In this study, we examined the efficacy of scAAV9/HEXM IV injections in 6 wk old Sandhoff disease (SD, β-subunit knock-out) mice at two doses: 2.5E 12 vg (LOW, n=17) or 1.0E 13 vg (n=15). Another cohort (n=16) received IV mannitol (3g/kg) prior to LOW injection. Some mice from LOW cohorts were euthanized at 16 wk for tissue comparisons to untreated SD mice; the remainder were monitored until the humane endpoint. Analyses of survival, behaviour and biochemical parameters were performed. Untreated SD mice had a 16 wk humane endpoint; subsets from the scAAV/HEXM treatment groups are surviving past 52 wk, a highly significant survival benefit. Analyses are ongoing. Preliminary results show that scAAV/HEXM delayed onset of the SD phenotype particularly in combination with IV mannitol. This study is the first to show an IV gene transfer using a scAAV/HEXM vector can provide survival and behavioural benefit in adult SD mice.

3-C-50 Redox switch in Neuronal Autophagy and apoptosis: Implication of Thioredoxin system

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Protein aggregation is a hallmark of neurodegenerative diseases (ND). Oxidative stress represent a major inducer of protein damage in ND pathology. Neurons have adapted a protective mechanism known as autophagy (self-digestion) that will potentiate cellular survival during early timepoints of stress. However, prolonged or severe oxidative damage of proteins will switch autophagy to apoptosis; a

common mechanism of neuronal cell death in ND. The underlying molecular system controlling the autophagy-apoptosis switch mechanism remains to be identified. In this project the involvement of cytoplasmic Thioredoxin (Trx) system in cell death was investigated. Trx protein is a major electron donor for reduction of oxidized proteins. Trx is oxidized but is reduced by TrxR. We used an in vitro model of SH-SY5Y neurons subjected to 6hr of serum starvation. This results in induction of autophagy which is quickly replaced with apoptosis and significant cell death. Upon pharmacologic inhibition or downregulation of TrxR, cell viability was further compromised. This was associated with decreased autophagy and intracellular accumulation of misfolded proteins. Further analysis revealed that TrxR deficiency results in oxidative inactivation of lysosomal Cathepsins. This study demonstrates for the first time the involvement of Trx system in the interplay between autophagy and apoptosis and the mechanism is through the redox regulation of lysosomal cathepsins. This opens a new avenue for developing novel therapeutic strategies for neurodegenerative disease where lysosomes are dysfunctional.

3-C-51 Myeloid cell-derived IL-1beta triggers CNS endothelial cell activation and autoimmunity.

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Interleukin 1beta (IL-1β) is a proinflammatory cytokine that plays key roles in host defense against pathogens. While IL-1β is important for homeostasis, some environmental and genetic factors involving the IL-1 system have been associated with the development of autoimmune diseases such as multiple sclerosis (MS). MS and its animal model, experimental autoimmune encephalomyelitis (EAE), are characterized by cognitive and motor deficits that are preceded by the apparition of demyelinating inflammatory lesions in the CNS. However, the precise mechanisms by which IL-1β participates in autoimmunity remain unclear. Until now, IL-1β has been linked to the maturation of Th17 cells, a subset of lymphocytes that is required for EAE. Nonetheless, the action of IL-1β on lymphocytes is not by itself sufficient to trigger CNS autoimmunity because mice lacking the IL-1 receptor type 1 (IL-1R1) in their hematopoietic cells have a similar disease course compared to controls. Here, using MOG35-55 EAE mice, we show that IL-1β is produced by neutrophils and monocyte-derived macrophages as a result of their migration across the CNS endothelium. We further found that CNS endothelial cells express high levels of IL-1R1 and, upon activation with IL-1β, release proinflammatory cytokines and chemokines that are essential for EAE development (e.g. IL-6, GM-CSF, CCL2). Finally, we demonstrate that the transfer of IL-1β-producing myeloid cells on the spinal cord of IL-1β-deficient mice, which are EAE resistant, is enough to trigger the recruitment of recipient lymphocytes to the spinal cord and EAE.

3-C-52 Dysfunctional decision-making processes in Parkinson's patients playing a strategic game

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During Rock-Paper-Scissors (RPS), each player's actions and associated outcomes change dynamically based on the opponent's actions. RPS requires inhibiting one action in favour of another; impulsivity results in a tendency to produce habitual actions without adequately computing reward history. Patients with Parkinson's Disease (PD) show changes in reward-learning, and dopaminergic agents (DA) increase

learning rates in reward guided tasks, potentially contributing to the occurrence of impulse control disorders in patients. We propose a novel paradigm to characterize choice patterns, and investigate the differential effects of DA, on motor and cognitive function during RPS in PD. PD patients (stage 1-3) and age-matched controls competed in a visuosaccadic game of RPS against a computer opponent that exploited biases in player's choice patterns. To dissociate cognitive from motor effects during RPS, results were contrasted with a control task that was similar to RPS in terms of sensory input, motor output, and reward rate. Choices were indicated with either a saccade or a button press. Each group completed 2 sessions; PD patients on- and off- DA. The PD group was more variable than controls, had faster reaction times, and showed a directional bias during RPS, which did not differ on- and off- DA. Overall reward rate was similar among PD patients and controls during RPS, but tended to be higher in patients off- compared to on-DA. Modeling of choice patterns will be critical to understanding how DA modulate learning rates during RPS, and developing biomarkers of impulsivity.

3-C-53 RHBDL4-mediated cleavage of the amyloid precursor protein reduces Amyloid-beta generation

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Since the recognition of Alzheimer disease (AD) in the early 20th century, the disorder has been a major health and socio-economic burden. Despite intensive research, so far no effective prevention of AD exists. Toxic amyloid-beta (Aβ) peptides are one of the hallmarks of AD pathology. They are generated from the amyloid precursor protein (APP) by two sequential cleavages. Lowering Aβ levels is one of the goals of therapeutic strategies. Rhomboid proteases are a conserved class of intramembrane proteases, which cleave their substrates within transmembrane and ectodomain regions. The human rhomboid-related protein 4 (RHBDL4) resides in the endoplasmic reticulum (ER) and was linked to protein degradation. We found that RHBDL4 efficiently cleaves APP in HEK 293T cells. Several cleavages occur in the APP ectodomain, leading to the generation of 70-73 kDa N-terminal fragments and multiple 10-25 kDa C-terminal fragments as determined by western blot analysis. Inhibition of other known APP processing enzymes (α-, β- and γ-secretases) did not affect production of RHBDL4-specific APP fragments, indicating that secretases are not involved in RHBDL4-mediated APP cleavage. Importantly, RHBDL4 leads to a reduction in Aβ peptide levels. Analysis of human brain tissue from AD cases and age-matched controls revealed an increase in RHBDL4 mRNA and protein levels, which may be a protective, compensatory response to accumulating Aβ. Thus, our results suggest a new processing pathway for APP, which removes it from amyloidogenic processing and therefore reduces Aβ levels.

3-C-54 Supervised learning improves the ability of MEG to detect Alzheimer's disease

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The preclinical detection of Alzheimer's disease (AD) would allow for the timely application of treatment, and is expected to be increasingly important as treatments improve. At present, magnetoencephalography (MEG) can distinguish individuals with moderate AD (average mini mental state exam (MMSE) score < 20) from age-matched healthy controls (HC) with 85% accuracy (Poza, 2007) based upon the frequency content (power spectral density; PSD) of brain activity measured in the resting-state. Herein we extend the capabilities of MEG to distinguish individuals with mild AD (average

MMSE score = 25) from HC by using the PSD as input to a supervised machine learning algorithm (support vector machine; linear kernel). Should our results hold for a larger sample size (20/21 subjects classified correctly in this study), MEG combined with machine learning may hold promise for the preclinical detection of AD. Poza, J. (2007), 'Extraction of spectral based measures from MEG background oscillations in Alzheimer's disease', Medical engineering & physics, vol. 29, no. 10, pp. 1073-1083.

3-C-55 Histopathological studies of the Effects of Combined Administration of Duovir-N and Vitamin E on the Cerebellum of Wistar rats.

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Duovir-N is a combination of three drugs (lamivudine, zidovudine and nevirapine) used for pre-exposure prophylaxis and management of Human Immunodeficiency Virus infection in sub-Saharan Africa. The objective of this research work was to investigate the potential Ameliorative effect of Vitamin E on Duovir-N induced toxicity on the cerebellum of Wistar rats. Twenty Wistar rats were used for this study. The rats were divided into 4 groups of 5 rats each. Group A served as the control, while group B were administered with 9.28 mg/kg of Duovir-N, group C received 9.28 mg/kg of Duovir-N and 10 iu/kg of E and group D received 10 iu/kg of Vitamin E. Drugs were administered twice daily for 30 days. The rats were sacrificed using the chloroform inhalation method and their cerebellum harvested, processed and stained using haematoxylin and eosin method and paraffin impregnated Glial Fibrillary Acidic Protein (GFAP) immunochemistry method. The slides were viewed under light microscope. Results showed that the cerebella were affected with moderate to severe shrinkage, distortion of the Purkinje cells and increased expression of GFAP in the treatment group B when compared with group C that received both Duovir-N and Vitamin E. Group A and group D that received distill water as control and Vitamin E respectively had normal slides. The drug Duovir-N distorts the histology of the cerebellum: Vitamin E has the potential of ameliorating this histological distortion. Key words; Duorvir-N, Cerebellum, Vitamin E , Human Immunodeficiency Virus.

3-C-56 Neuroprotective and anti-inflammatory roles of estrogenic receptors 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. In order to better understand the role of the estrogen receptors ERα, ERβ and GPER1 in neuroprotection and immune modulation in the MP, adult male C57BL/6 mice received different combinations of the following products twice a day: 17β-estradiol (1µg), G1 (5µg) GPER1 agonist, G15 (10µg) GPER1 antagonist, PPT(1µg) ERα agonist, DPN (3µg) ERβ agonist and ICI 182,780 (25µg) ERα/β antagonist. On day 5, 4 injections of MPTP (4.75mg/kg) were administrated. On day 10, 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, monocytic cell pro-inflammatory polarization, nuclear factor-kappa B (NF-κB) response, nitric oxide and pro-inflammatory cytokines production following 1-methyl-4-phenylpyridinium (MPP+) treatment were also measured for each condition. Overall, our results suggest that estrogen therapy may help prevent the loss of DA neurons, the infiltration of macrophages and pro-inflammatory responses, mainly involving GPER1.

3-C-57 Investigating the Role of CDNF, MANF, and BDNF as Biomarkers and Therapeutic Targets for Parkinson's Disease.

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Parkinson's disease (PD) is a common neurodegenerative disorder primarily affecting the aging population and is characterized by the significant degeneration of dopaminergic (DAergic) neurons in the substantia nigra. Because neurotrophic factors (NTFs) are naturally occurring proteins that promote the survival, differentiation and maintenance of neurons, we used a human neuroblastoma cell line to investigate the effects of mood stabilizers on the expression of three NTFs: brain derived neurotrophic factor (BDNF), conserved dopamine NTF (CDNF) and mesencephalic astrocyte-derived NTF (MANF). SH-SY5Y cells were treated with 3 mM lithium (LiCl) or 1 mM valproic acid (VPA). The resultant mRNA expression of CDNF, MANF, and BDNF were measured using RT-qPCR. LiCl administration significantly increased mRNA expression of MANF, CDNF, and BDNF upon differentiation of SH-SY5Y cells. Administration of VPA increased mRNA expression of the three NTFs in differentiated and undifferentiated SH-SY5Y cells. The results suggest that LiCl and VPA may ameliorate the symptoms of PD by upregulating certain NTFs. Future research and clinical implications of this project involve analyzing expression of these NTFs in patients with PD and other neurodegenerative disorders. This study allows us to elucidate the neuroprotective role of CDNF, MANF, and BDNF in the nervous system and their potential involvement as a biomarker for PD. This research is funded by NSERC.

3-C-58 Exogenous Dopamine Application and Synaptic Plasticity in the Normal Globus Pallidus

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The basal ganglia (BG) output nucleus, globus pallidus internus (GPi), receives and integrates information from the direct and indirect pathways and gates information relayed outside of the BG. Changes in synaptic plasticity may act as this gate; slice work indicates that when the indirect pathway is inactive, direct pathway activity can be potentiated by dopamine (DA), whereas indirect pathway activation can depresses direct pathway GABA release. Field evoked potentials (fEPs) have been used to demonstrate synaptic potentiation in the BG of Parkinson's disease (PD) patients when exogenous DA is administered. Here, we test the effects of high frequency stimulation (HFS) on fEPs in 2 healthy non-human primates in the GPi before and after application of the DA precursor L-Dopa. Neuronal activity and fEPs were recorded from 3 electrodes in GPi for 5 minutes using 0.25Hz test pulses from a 4th electrode, then HFS (four 2s trains, 100Hz, 100uA) was delivered through the stimulating electrode. Post HFS, 0.25Hz pulses resumed and fEPs were monitored for 15 minutes to measure changes in synaptic efficacy resulting from HFS. 20mg/kg L-Dopa was given orally and allowed to metabolize for 45 minutes. fEP testing before and after HFS was repeated to measure the DA dependent changes in the normal

state. Following HFS, fEPs underwent depression, both in the baseline and exogenous DA state. This result suggests normal dopaminergic tone in the BG does not result in potentiation, and that potentiation observed in patients with PD treated with DA is a pathological response.

3-C-59 Characterization of the effects of FDA-approved drugs on human cells: A potential treatment for C9ORF72 ALS cases.

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder causing progressive degeneration of motor neurons. Several genes are implicated in the pathology of ALS, including C9ORF72, which contains a repetition of the six nucleotides, GGGGCC, in the first intron of the latter gene. In patient tissues, the expanded GGGGCC repeat seems to cause RNA foci and production of dipeptides and induce a loss of expression of C9ORF72. In C. elegans, both the loss of function and RNA toxicity were shown to be detrimental to neurons. Using C. elegans, 4,000 FDA-approved drugs were screened to identify molecules that can alleviate the neurotoxicity caused by a loss of function of C9ORF72 and by the presence of a pathogenic GGGGCC repeat RNA. Eight compounds were shown to alleviate the toxicity of both models and were chosen to be tested in patient-derived cells. These cells exhibit abnormal RNA expression and presence of dipeptides. The goal of this project is to characterize the effects of the molecules identified in C. elegans in patient-derived cells. If the project is successful, new therapeutic avenues for ALS could be discovered and more will be understood about C9ORF72 modes of toxicity.

3-C-60 Cadherins mediate cocaine-induced synaptic plasticity and behavioural conditioning

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Drugs of abuse alter synaptic connections in the 'reward circuit' of the brain, which leads to long-lasting behavioral changes that underlie addiction. Here we show that cadherin adhesion molecules play a critical role in mediating synaptic plasticity and behavioral changes driven by cocaine. We demonstrate that cadherin is essential for long-term potentiation (LTP) in the ventral tegmental area (VTA), and is recruited to the synaptic membrane of excitatory inputs onto dopaminergic neurons following cocaine-mediated behavioral conditioning. Furthermore, we show that stabilization of cadherin at the membrane of these synapses blocks cocaine-induced synaptic plasticity, leading to a significant reduction in conditioned place preference induced by cocaine. Our findings identify cadherins and associated molecules as targets of interest for understanding pathological plasticity associated with addiction.

3-C-61 Assessing outcomes of an Endothelin-1 induced stroke injury in an APP transgenic rat

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While traditionally regarded and treated as distinct conditions, the roles of Alzheimer's disease (AD) and stroke as interacting ailments has attracted interest, though no conclusive pathophysiological link has yet to be determined. Using an in vivo rat model, it is hypothesized that following ischemic stroke, a transgenic rat model carrying human amyloid precursor protein (APP) mutations will display enhanced

amyloid-beta (Aβ) deposition, heightened neuroinflammation, and more severe cognitive decline. To model AD pathology, our study utilizes a genetically engineered rat model exhibiting mutations in APP; this model overproduces Aβ. To model ischemic stroke, a unilateral striatal injection of endothelin-1, a potent vasoconstrictor, is utilized. The proposed models are studied both in combination as well as singularly over a period of three months post-stroke, utilizing various behavioural and histological techniques. Preliminary results from our laboratory suggest that in the presence of amyloid deposition, facets of stroke including infarct size and the degree of neuroinflammation are heightened. These pathological effects are shown to be translated into behavioural deterioration in rodent models of AD and stroke. Overall, with a better understanding of the mechanistic roles of stroke and AD pathology on resultant cognitive impairment, it may be possible to employ strategies to minimize post-stroke cognitive burden. Further studies are required to truly understand the interactions between Aβ toxicity, ischemic stroke damage, and neuroinflammation.

3-C-62 The 3xTG-AD and 5XFAD mouse models of Alzheimer's disease show differences in signal detection and response bias on an automated odour discrimination task

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Early symptoms of Alzheimer's disease (AD) include deficits in olfactory function. We tested two transgenic mouse models of Alzheimer's disease, the 3xTg-AD and the 5XFAD mice, and their B6129 and B6SJL controls, on an odour detection task at six months of age. The mice were presented with decreasing concentrations of ethyl acetate in a go no-go operant olfactometer task. Female 3xTg-AD mice where less able to detect the odour than their female B6129 controls, and showed a more liberal response bias. The male 3xTg-AD mice did not differ from the male B6129 controls on either of these measures. The 5XFAD mice showed the same ability to detect the odour as the B6SJL controls, but show a less liberal response bias than controls. Among both the 5XFAD and B6SJL mice, females were better able to detect the odour, while males showed a more liberal response bias. These finding suggest that female, but not male, 3xTg-AD mice show impaired olfactory function compared to their wildtype controls, while no impairment was found in the 5XFAD mice. The differences in response bias between female 3xTg-AD and their controls, and between 5XFAD of both sexes and their controls, suggests there are alterations in cognitive function in these AD models which affect performance on even a relatively simple olfactory task.

3-C-63 TAU Modulates BDNF Expression and Mediates Aß-Induced BDNF Down-Regulation in Animal and Cellular Models of Alzheimer's Disease

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In Alzheimer's disease (AD), soluble tau is hyperphosphorylated, and some of this population aggregates and precipitates as neurofibrillary tangles (NFTs). This pathological tau is believed to cause neurodegeneration, although a precise toxic mechanism is not well understood. Our hypothesis was that pathological tau down-regulates brain-derived neurotrophic factor (BDNF), a pro-survival protein that is lost in AD. Using qRT-PCR of cortical tissue from transgenic mice (8c-het and hTau mice) over-expressing normal (not mutated) tau, we found a significant reduction in BDNF mRNA compared to controls. The 8c-het mice do not develop NFTs, while the hTau mice do exhibit NFTs, yet both models significantly down-regulate BDNF. We also found a significant reduction in BDNF and BDNF transcript IV

in wild-type tau (hTau40) transfected human neuroblastoma (SH-SY5Y) cells compared to controls. Lastly, we found that APP23 mice, which over-express soluble Aβ, also have significantly reduced BDNF mRNA. When crossed with TauKO mice, the resulting APP23xTauKO animals have BDNF expression that is not statistically different from wild-type animals. Our results demonstrate that excess wild-type tau can down-regulate BDNF, and that neither a mutation in tau nor NFTs are required for toxicity as measured by BDNF expression. Furthermore, the partial rescue of BDNF levels by tau knockout suggests that tau contributes to Aβ-induced BDNF down-regulation. Thus, loss of BDNF may mediate tau neurotoxicity, which has profound implications for therapeutic intervention in AD and tauopathies.

3-C-64 Dopamine D3 receptor activity and its downstream signaling targets are altered within the basolateral amygdala following chronic opiate exposure

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The rewarding effects of opiates contribute to the formation of potent memories that link feelings of euphoria with the drug taking experience. These memories are encoded in the basolateral amygdala (BLA), which has previously been shown to be sensitive to opiate exposure. The dopamine D3 receptor (D3R) is expressed in limbic regions, and is involved in reinforcing motivational and emotional functions. Further, D3R activation is linked to Cdk5 and calcineurin, both of which play roles in synaptic plasticity and formation of conditioned reward memories. We propose that chronic opiate exposure alters expression of intra-BLA D3Rs and downstream targets in the context of associative reward memory formation. We assessed changes to D3R, calcineurin and Cdk5 with western blotting in rats. Opiate dependence and withdrawal resulted in a downregulation of D3R, and an upregulation of calcineurin and Cdk5. The functional significance of these results was tested in a conditioned place preference procedure. Intra-BLA D3 activity was not necessary for the formation of opiate reward memories until after the induction of opiate dependence, when D3 antagonism blocked the acquisition of a place preference. Co-administration of a D3 antagonist with calcineurin or Cdk5 antagonists reversed this effect, indicating that these molecules may be the mechanism underlying sensitivity of associative memory formation to D3R antagonism in dependent/withdrawn animals. This work points to a role of intra-BLA D3 activity in the development of disturbances in reward memory function during opiate dependence.

3-C-65 Cerebral aquaporins (AQPs) and their co-localised potassium channel as potential drug targets and/or biomarkers in Temporal Lobe Epilepsy (TLE)

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AIMS Temporal lobe epilepsy (TLE) is often refractory to anti-epileptic drugs (AEDs) and results in atrophied sclerotic cerebral tissue. This study aims to determine the expression and functional trafficking profile of the aquaporin (AQP) water channels and potassium channel in post mortem controls and in sclerotic and non-sclerotic hippocampi of TLE patients. METHODS Quantitative real-time qRT-PCR of AQP1, 3, 4, 5, 8, 9, 11 and KAB-2/kir4.1 on ten sclerotic, seven non-sclerotic TLE human patient and ten post-mortem control samples. Western blotting analysis of the expressed AQP mRNAs was then conducted. AQP 1, 4, 5 and 9-GFP fusion proteins in HEK293 cell line and primary rat astrocytes were visualised using laser confocal microscopy. MALDI-MSI imaging and profiling will be used for proteomic analysis. RESULTS AQPs 1, 3, 4, 5, 8, 9 and AQP11 were expressed in both non-sclerotic and

sclerotic patient samples with AQP1, 4, 8 and 9 showing interesting differences compared to non TLE patients, reduced expression levels of kir4.1in sclerotic hippocampi were observed. All AQP-GFPs and endogenous AQPS showed rapid and reversible hypotonicity-mediated translocation to the cell membrane in HEK293 and primary astrocytes respectively. CONCLUSIONS This study shows, for the first time, that all investigated cerebral AQPs are present in the sclerotic and non-sclerotic hippocampi of TLE patients. The upregulation of AQP1, 4 and 8 accompanied by the down-regulation of kir4.1in sclerotic hippocampi may contribute to the progression of TLE and/or its resistance to AEDs. Further experiments

3-C-66 Personalized botulinum toxin type A therapy of bilateral upper limb essential tremor by multi-sensor kinematic technology

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Essential tremor (ET) causes functionally and socially debilitating tremor in the upper limbs. Focal therapy can reduce severity though is frequently associated with adverse effects and lack of functional benefit. This study aims to demonstrate that sensor technology can quantitate tremor biomechanics and can be solely used to individualize botulinum toxin type A injection parameters. 21 ET participants attended 6 study visits and received treatment in both upper limbs every 12 weeks, totalling 3 injection cycles, and attended a follow-up visit 6 weeks post-treatment. Clinical rating scales and kinematics to assess tremor and functionality were completed at each visit. Participants performed scripted tasks to capture unique tremor compositions using goniometers and torsiometers placed over arm joints. A dosing algorithm was used to calculate dosing and to select muscles. Wrist tremor severity during scripted tasks following the first treatment at week 6 demonstrated a statistically significantly reduction by 64.0%; elbow and shoulder tremors were significantly reduced by 58.2% and 33.6%, respectively. Relief of tremor was maintained 12 weeks following treatment at the time of re-injection. Handwriting and functional performance (FTM part B and C) were significantly improved following the third treatment. No significant adverse effects were reported though participants perceived mild weakness not functionally bothersome. Kinematic tremor assessments allow clinicians to standardize both multi-joint tremor assessments and injection parameter determinations.

3-C-67 Prohibition of Neogenin interaction with lipid rafts promotes functional recovery after ischemic stroke

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The dependence receptor Neogenin and its ligand, the repulsive guidance molecule a (RGMa), regulate apoptosis and axonal growth in the developing and the adult central nervous system (CNS). Here, we show that this pathway has also a critical role in neuronal death following stroke, and that providing RGMa to neurons blocks Neogenin-induced death. Interestingly, the Neogenin pro-death function following ischemic insult depends on Neogenin association with lipid rafts. Thus, a peptide that prevents Neogenin association with lipid rafts increased neuronal survival in several in vitro stroke models. In rats, a pro-survival effect was also observed in a model of ocular ischemia, as well as after middle cerebral artery occlusion (MCAO). Treatments that prevented Neogenin association with lipid rafts improved neuronal survival and the complexity of the neuronal network following occlusion of the middle artery. Toward the development of a treatment for stroke, we developed a human anti-RGMa antibody that also prevents Neogenin association with lipid rafts. We show that this antibody also

protected CNS tissue from ischemic damage and that its application resulted in a significant functional improvement even when administrated 6 h after artery occlusion. Thus, our results draw attention to the role of Neogenin and lipid rafts as potential targets following stroke.

3-C-68 Different Forms of Disinhibition Have Distinct Effects on Dorsal Horn Circuits

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Pain caused by damage to the nervous system (i.e. neuropathic pain) is a notoriously intractable condition. Increased spontaneous activity of somatosensory neurons has been found in animal models of neuropathic pain, and is thought to contribute to its debilitating nature. Reduced synaptic inhibition in the dorsal horn plays a role in the pathogenesis of neuropathic pain; however the mechanism through which this disinhibition manifests is not clear. We aimed to investigate differences between two potential mechanisms of disinhibition; reduced GABA transmission and chloride dysregulation. Using Morris-Lecar equations, we built a computational neural network that modelled touch sensitive circuits in the dorsal horn. We fit the model using relevant properties of the circuit, determined through multi-channel in-vivo recordings in adult male Sprague-Dawley rats. Our model was able to reproduce the effect of co-stimulation in different regions of the network's receptive field, and firing characteristics of excitatory and inhibitory neurons in the dorsal horn. Simulations of each mechanism of disinhibition determined that chloride dysregulation produced a pronounced increase in the spontaneous firing rate of neurons, whereas reduced GABA transmission did not. Similar results were found in-vivo, by pharmacologically inducing each form of disinhibition. This suggests that each form of disinhibition manifests in touch sensitive circuits in a fundamentally different way, and furthermore that chloride dysregulation is an important contributor to the development of neuropathic pain.

3-C-69 The role of PAR2 activation in the pathophysiology of synucleinopathies with emphasis on Multiple System Atrophy (MSA)

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Synucleinopathies such as Multiple system atrophy (MSA) are adult onset sporadic neurodegenerative diseases. Glial cytoplasmic and nuclear inclusions of α-synuclein in oligodendrocytes of patients with phenotypically varied MSA provided convincing evidence that MSA is a distinct clinicopathological entity. However, the molecular mechanisms underlying pathophysiology of MSA are not well understood and this has been hampering the design of a proper treatment. The proteinase activated receptor 2 (PAR2) is G protein-coupled receptor that requires proteolytic cleavage at the amino terminus to stimulate intracellular signaling cascade. In this work, we hypothesized that PAR2-mediated epigenetic upregulation of α-synuclein contributes to the pathogenesis of MSA. PAR2 has been stimulated with the selective agonist peptide, SLIGRL-NH2, in human oligodendrocyte cell line (MO3.13) that expresses endogenous α-synuclein. The cleavage of the receptor is visualized by calcium-mobilizing assay. Changes in α-synuclein expression is assessed by RT-qPCR, protein analysis methodology and imaging to detect aggregates. Human brain donated to research from patients suffering from MSA and with neuropathological confirmation of disease will be evaluated for levels of PAR2 and other related proteins downstream of its pathway. The overall goal of this project is to clarify the impact of signal transduction pathways triggered by PAR2 activation on the formation of glial cytoplasmic and nuclear inclusions of α-synuclein in oligodendrocytes and MSA.

3-C-70 LPS-Induced Blood-Brain Barrier Disruption: Assessing Lithium's Molecular and Therapeutic Effects

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Bipolar disorder (BD) is a debilitating mental illness affecting approximately 2% of the world's population. The current options in treating the disease, is the use of lithium, a known effective mood stabilizer along with antipsychotic drugs. Inflammation of the blood-brain barrier (BBB) combined with the subsequent passage of invasive, pro-inflammatory cytokines into the central nervous system have recently arisen as vital components in the pathophysiology of a number of neuropsychiatric diseases. However, in the case of BD, this mechanism remains understudied. We aimed to fill this gap in knowledge by testing lithium's ability to prevent disruption in BBB induced by inflammation. Our study administered lipopolysaccharides (LPS) to male Sprague-Dawley rats (n=20) to disrupt BBB 24 hours before sacrifice, and administered 8 days of pre-treatment with lithium (n=10) in preventing this disruption. Sodium fluorescein (NF) was administered 20 minutes prior to sacrifice to quantify the degree of BBB disruption. Through NF assays, we were able to show that lithium partially prevented the disruption in BBB in several areas of the brain, including the prefrontal cortex, cortex, striatum, and whole brain samples. The results suggest a mechanism of lithium's therapeutic action for BD, by preventing the inflammation in BBB. Our novel approach of studying BD through BBB inflammation promises to be an avenue for better understanding BD's pathophysiology, creating a more accurate model, and advancing research into new treatments for this illness. This work is funded by OMHF.

3-C-71 Traumatic brain injury induces progressive and degenerative changes resembling motor neuron disease that are exacerbated by pathological TDP-43

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Motor neuron disease (MND) and is characterized by the progressive death of motor neurons, degeneration of the corticospinal tract, and the presence of transactive response DNA binding protein 43 (TDP-43) pathologies. To date the aetiology of MND remains largely unknown. Traumatic brain injury (TBI) has been linked to the later onset of MND, however a causal relationship between these conditions remains controversial. As such, here we administered experimental TBI via the fluid percussion model to rats and assessed for progressive MND-like abnormalities. Volumetric MRI found that TBI resulted in progressive atrophy of the motor cortices , and tensor-based morphometry and diffusion-weighted imaging revealed progressive degeneration within the corticospinal tracts. Rats given a TBI also had a reduction in neurons and an increase in pathological TDP-43 in the motor cortex, fewer motor neurons in the spinal cord, muscle atrophy, and motor impairments. To further examine the potential role of pathological TDP-43 in this process we next administered TBI to transgenic mice that overexpress TDP-43 or wild-type mice. All TBI mice had pathological TDP-43 relative to their sham-controls, with TDP-43 + TBI mice having more than all other groups. While all mice given a TBI had significant neuronal death, it was worse in TDP-43 + TBI mice. TDP-43 + TBI mice also had worse cognitive and motor deficits compared to their wild-type counterparts. These findings suggest that TBI can induce a progressive disease process resembling MND and that TDP-43 pathologies may contribute to these effects.

3-C-72 Effect of Normal and Parkinson's Disease-Mutant Alpha-Synuclein on Synaptic Vesicle Recycling in Human CNS Presynaptic Terminals

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α-Synuclein has been associated with a number of severe and progressive human brain disorders that have been grouped as α-synucleinopathies. Parkinson's disease (PD) is a key member of this group and several cases of the disease have been attributed to α-synuclein point mutations including A30P and A53T. α-Synuclein is known to be concentrated at presynaptic terminals and, while its precise presynaptic role remains elusive, the protein has been associated with synaptic vesicle (SV) recycling. Altered SV recycling was observed with normal and PD mutant α-synuclein overexpression in rodent tissue (Nemani et al. 2010). To explore if these effects also occur in humans, we introduced normal and mutant α-synuclein into isolated live human synaptosome (SSM) nerve terminals. SSMs were obtained from human cortex removed for epilepsy surgery. The test proteins were introduced into the SSMs by cryoloading (Nath et al. 2014) and SV recycling was assessed by depolarization-induced FM-dye uptake. Introduction of wild type or A53T mutant form of the protein had no detectable effect on FM-uptake but we did observe a small, but statistically significant reduction with A30P. Thus, our results did not reproduce in human terminals the significant pathological effects of α-synuclein on SV recycling observed in rodents and suggest that the evaluation of the cellular basis of α-synucleinopathies may require study using human-specific experimental models.

3-C-73 The effects of microglia-mediated inflammation on neuronal development in vivo

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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. Moreover, IL-1β levels are greatly increased following LPS treatment. Preventing differentiation of myeloid lineage cells, which includes microglia, by morpholino oligonucleotide knockdown of the Pu.1 transcription factor eliminates the effects of LPS, indicating a central role for microglia in this process. We used Tg(Elav3:H2B-GCaMP6s) transgenic fish, in which the genetically encoded 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. Using resonance scanners 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. These experiments will provide insights into the mechanisms that contribute to neurodevelopmental defects caused by microglia-mediated inflammation. Our findings will inform translational studies that may help to mitigate or prevent neurodevelopmental and neuroinflammatory disorders. Funded by CIHR Vanier Award (NAIF), FRQS Research Chair (ESR).

3-C-74 The role of thalamo-motor fibre damage in overt motor responses in disorders of consciousness.

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The differential diagnosis of disorders of consciousness (DOC) is made on the basis of bedside behavioral scales, such as the Coma Recovery Scale-Revised (CRS-R). The patient's capacity to respond to

multisensory stimulation determines whether the patient is diagnosed as being in a vegetative state (i.e. reflexive responses) or in a minimally conscious state (i.e. intentional responses). Recent neuroimaging studies have stressed the problems related to this reliance on external behavior: if an aware patient was unable to produce overt responses due to a motor dysfunction, they would be misdiagnosed as VS. It has been suggested that damage to thalamo-motor fibres may be related to a lack of purposeful motor behaviour following brain injury. Here we used diffusion tensor imaging to reconstruct and assess the structural integrity of those pathways in DOC patients, as well as its relationship with the level of external responsiveness they show. Global CRS-R scores were correlated with the FA values of the left (rho=.658, p=.008) and right (rho=.571, p=.026) thalamo-motor tracts. Furthermore, patients were grouped into one of two categories: responsive (MCS+EMCS) /non-responsive (VS). These groups showed a significant difference in FA values of the thalamo-motor tracts (F(1,13)=5.230, p=.04). Our results suggest a motor involvement in the extent to which DOC patients respond. Damage to this network could thus interfere with the correct diagnosis of their condition.

3-C-75 History of Traumatic Brain Injury Moderates Relationships Between Polygenetic Risk and Neural Substrates of ADHD Symptoms

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Attention Deficit/Hyperactivity Disorder (ADHD) is both a risk factor for and major sequelae of traumatic brain injury (TBI) in youth. The objective of this study was to examine whether 1) genetic risk for ADHD and 2) altered brain structure; differentially predict ADHD symptoms in youth with and without a history of TBI. In a large sample of youth we investigated interactions between history of TBI and polygene risk scores (PRS) with ADHD symptoms (TBI=334, NoTBI=2174) as well as between history of TBI and neuroimaging phenotypes relevant to ADHD, namely frontal white matter tract fractional anisotropy (FA) with ADHD symptoms (TBI=133, NoTBI=709). Youth with a history of TBI reported an increased number of ADHD symptoms compared to those without a history of TBI ($p<5e-07$). PRS was associated with ADHD in those without a history of TBI ($p<5e-08$) but not in youth with history of TBI ($p>0.05$, $pInt<0.01$). Common neural substrates were associated with ADHD in those with and without a history of TBI; however the direction of effect was different. FA in the genu of the corpus callosum (GCC) and left anterior corona radiate (ACR) was positively associated with ADHD symptoms in youth without a history of TBI ($pGCC<5e-07$, $pACR<5e-03$) but negatively associated with symptoms in youth with a history of TBI ($pGCC<5e-04$, $pACR<5e-02$; $pIntGCC<5\ e-06$, $pIntACR<5\ e-03$). These results suggest that ADHD associated with TBI is a result of mechanical insult to similar neural pathways that have distinct effects from those affected by genetic risk in developmental ADHD.

3-C-76 Differential Effects of Hippocampal Kindling in Young and Aging Mice

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Aging is associated with an increased incidence of seizures and the development of epilepsy. Similarly, the incidence of stroke (hemorrhagic and ischemic), trauma and dementias increases with advanced age. Whether aging is associated with higher seizure susceptibility in the absence of the above pathologies remains unclear. We used hippocampal kindling as a model to explore this issue. The kindling induced epileptogenic process is not associated with evident brain injury, which will allow us to dissociate the effects of age and brain injury, and with this model the epileptogenic process can be

reliably monitored in individual animals over time. We kindled young and aged mice (C57BL/6, 2 and 20 month-old) via daily hippocampal stimulation and monitored seizure activity via video and EEG recordings. The number of daily stimuli required to induce five consecutive stage 5 motor seizures was similar between young and aged mice, however, the aged mice developed stage 5 seizures with fewer daily stimulations than the young mice. In addition, the primary discharge duration associated with stage 5 motor seizures was longer in aged mice than in young mice. Our observations suggest higher seizure/epilepsy susceptibility in aged mice relative to young mice. Data analysis is in progress to explore whether hippocampal EEG rhythms and interictal spikes differ between kindled young and aged mice. Supported by CIHR, NSERC, Eplink of Ontario Brain Institute

3-C-77 Characterization of Anatomical Brain Recovery after Treatment with Metformin in Hypoxia-Ischemia Mouse Model of Childhood Brain Injury Using Micro-MRI

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Perinatal hypoxic-ischemic (H/I) brain injury is often associated with long-term disability. Recently, it has been shown that treatment with metformin results in activation of neural precursor cells (NPSc) and leads to neural repair and functional recovery in a mouse model of perinatal H/I insult (Dadwal et al, 2015). The goal of the present study was to further characterize this model in order to shed more light on metformin stimulated brain repair processes and to better understand brain structural changes underlying previously observed behavioural recovery. Briefly, to induce the H/I injury, left common carotid artery was ligated at postnatal day 8 (P8) and pups were subjected to 1h hypoxia. Metformin was delivered to the pups from P9 to P15 through the milk of lactating mothers, which were implanted with mini-osmotic pumps releasing metformin. 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=5) and mice with H/I injury that were given metformin (n=8) were evaluated ex vivo at P23 using high-resolution (40µm-iso) anatomical micro-MRI (Nieman et al, 2006). In addition to an expected reduction in volume in the left hemisphere, a relative, regional increase in volume in the contralateral hemisphere was observed in all mice with the H/I injury. This relative increase was more pronounced in mice treated with metformin. No major differences were observed in metformin-treated and untreated control mice, suggesting that the effects of metformin become important in the context of injury.

3-C-78 Entorhinal tau pathology decouples hippocampal and prefrontal oscillations without impairing associative memory

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Alzheimer's disease (AD) is a neurodegenerative disorder associated with progressive memory loss and the deposition of proteinaceous substances including the intracellular aggregation of tau proteins. Entorhinal neurons are the first to be affected by tau aggregates, and in humans this initial stage precedes detectable memory impairments by many years. These tau aggregates impair various properties of single neurons and synaptic plasticity. Yet, given dense reciprocal connectivity of the entorhinal cortex with the hippocampus and many neocortical regions, the disruptive effect may also extend to these yet pathology-free regions, resulting in dysfunction of a long-range circuit underlying memory processes. To address this point, we examined couplings of local field potentials between two

entorhinal efferent regions, the dorsal hippocampus (dHPC) and medial prefrontal cortex (mPFC) while male rats that over-expressed mutated human tau (P301L) in the entorhinal cortex learned an associative memory. We found that entorhinal tau over-expression impaired stimulus-induced oscillatory couplings between the dHPC and mPFC. In particular, tau over-expression attenuated theta phase synchronization and theta-gamma amplitude correlation without affecting stimulus-induced oscillatory amplitude. In addition, the tau overexpression altered the network state associated with memory but did not impair memory performance. Thus, tau-induced dysfunction of entorhinal neurons resulted in abnormal hippocampal-prefrontal circuit operation before detectable memory impairments.

3-C-79 Childhood maltreatment is associated with a global impairment of oligodendrocyte function in the anterior cingulate cortex of depressed suicides

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Childhood maltreatment (CM) is a major risk factor for depression that strongly associates with suicidal behavior in adulthood. To gain insight into the neurobiological basis of these effects, we performed a transcriptome-wide analysis of gene expression in the anterior cingulate cortex (ACC) of depressed suicides with or without a history of CM, and psychiatrically normal individuals, obtained from the Douglas-Bell Canada Brain Bank. Using RNA-sequencing followed by Nanostring validation, we found that a large collection of genes related to myelin and oligodendrocyte function was specifically downregulated as a function of CM. We further investigated whether these molecular effects were associated with changes in myelination of individual fibers within the adjacent white matter. Using high throughput, high resolution imaging of myelin by Coherent anti-Stokes Raman Scattering (CARS), we found that small caliber axons of the ACC are less myelinated in depressed suicides with a history of CM. This was associated with decreased density of oligodendrocytes, as assessed by stereology. Further experiments are ongoing to investigate whether the effects of CM may be related to differential epigenetic regulation, in particular DNA methylation, of myelin gene expression. Altogether, these complementary approaches converge to highlight that CM leads to a global long-term impairment of oligodendrocyte function in the ACC. Considering the critical role of myelination in normal brain development, this may represent a key mechanism by which CM may have lifelong behavioral consequences.

3-C-80 Investigating Perivascular Changes and the Blood Brain Barrier in Fetal Alcohol Spectrum Disorder

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Fetal alcohol spectrum disorder (FASD) is a group of conditions that are characterized by physical and mental impairment in the offspring of women who consumed alcohol during their pregnancies. People with FASD have a higher incidence of epilepsy and it has been shown that exposure to alcohol in utero is followed by a reduction of glial cells from the somatosensory cortex in animals. Glial cells are crucial in providing structural and functional support to the blood brain barrier (BBB), a multi-cellular system that highly regulates the passage of molecules and ions in the central nervous system (CNS). Epilepsy has

been reported to be linked to BBB dysfunction; however it is yet unknown which condition precedes the other. Objective: To investigate blood brain barrier integrity in an FASD mouse model and study the role of astrocytic gap junction proteins in this disorder. Methods: In vivo fluorescence imaging following an intravenous (IV) injection of fluorescent dextran is used to show perivascular leakages in FASD mice and assess BBB integrity. Astrocytic levels of connexin 30, a gap junction subunit, is examined in FASD mice associated with BBB disruption using immunofluorescence. Results: Preliminary results suggest a reduction of BBB integrity in FASD mice. This study is significant in the development of therapeutic strategies for the treatment of FASD related hyper-excitability and improving our understanding of the mechanisms involved in epileptogenesis.

3-C-81 OTUD7A is a novel candidate driver gene of neurodevelopmental abnormalities in the 15q13.3 microdeletion syndrome

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The 15q13.3 CNV microdeletion is associated with high risk for epilepsy, intellectual disability, schizophrenia and autism spectrum disorder (ASD), and most reported cases are heterozygous. However, the neurodevelopmental abnormalities underlying the clinical phenotypes remain unknown. To study this, we are using a heterozygous 15q13.3 microdeletion mouse model that displays characteristic behavioural features of 15q13.3 syndrome, including epilepsy, increased stereotyped behaviour and deficits in spatial learning and memory. To understand how these behavioural abnormalities arise, we analyzed postnatal neuronal morphology, which revealed alterations in dendritic arborization and spine morphology in excitatory cortical pyramidal neurons. Additionally, preliminary biochemical analyses revealed altered baseline protein levels of the synaptic immediate early gene Arc in the cortex of heterozygous mice. Electrophysiological experiments will be conducted next to determine whether these morphological and biochemical changes correlate with changes in neuronal function. To understand the pathophysiology of 15q13.3 syndrome, we are dissecting candidate disease-causing genes using whole genome sequencing and human transcriptome data. Preliminary whole genome sequencing of ASD probands and their families revealed inherited and de novo variants in one of the genes within the 15q13.3 region, OTUD7A. Future work will focus on determining whether loss of OTUD7A can account for the observed morphological defects in the mouse model and elucidating the role of this gene in neurodevelopment.

3-C-82 The Biochemical and Behavioural Effects of Tyrosine Hydroxylase Overexpression in Transgenic Mice

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Oxidative stress is believed to contribute to the neuropathology of Parkinson's disease, which is characterized by a profound loss of dopamine (DA) and noradrenaline neurons. The rate-limiting enzyme in the production of both DA and noradrenaline is tyrosine hydroxylase (TH), an enzyme specifically expressed in catecholamine cells. As small amounts of reactive oxygen species are known by-products of its reaction, TH has the capacity to contribute to pathological conditions. Dysregulation of TH activity can also lead to the accumulation of free cytosolic DA, known to be neurotoxic. Here, we have developed a mouse overexpressing TH with the aim of assessing if increased levels of active TH could

contribute to oxidative stress. Transgenic mice (TH-HI) possess six total copies of the TH gene, resulting in a 3-fold increase in both mRNA and TH protein levels. The increase in TH protein levels is accompanied by a 2-fold increase in functional TH activity, as assessed by L-DOPA accumulation, in both young and adult mice (4 and 10 weeks). Importantly, at 4 weeks of age, striatal DA tissue content is also significantly higher in TH-HI mice; however, there is no significant change in DA content at 10-20 weeks. Still, striatal content of metabolites remains significantly higher at both ages, as does the ratio of metabolites to DA. Our results may indicate an increased DA turnover in TH-HI mice and may be predictive of increased oxidative stress. We aim to use this model to further evaluate if increased levels of TH can lead to oxidative stress and catecholaminergic cell loss in vivo.

3-C-83 Extensive white matter pathology in aged wildtype and APP transgenic rats used to model post-stroke dementia

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Stroke is a potent risk factor for developing dementia, yet a treatable mechanistic link between the two conditions remains elusive. In search of such links we study how a rat's brain rendered vulnerable to developing signs of Alzheimer's disease handles the challenge of a stroke. We use transgenic rats that express the human form of the amyloid precursor protein central to Alzheimer's disease pathology. We let these animals and wildtype counterparts survive for 9 months after induction of a small subcortical stroke by intracerebral injection of the vasoconstrictor endothelin-1, or injection of saline in control subjects. Animals are monitored for learning and memory performance and their brains are removed for histological analyses to identify and quantify pathologic processes at 15 months of age. The transgenic animals show a deficit in learning new tasks compared to wildtype controls, which does not seem to be exacerbated by stroke. Immunohistological analysis has revealed an abundance of activated OX-6 positive microglia in all major white matter tracts across experimental groups. Quantification of OX-6 positive microglia demonstrates that white matter inflammation tends to be more severe in transgenic rats. This finding is in line with clinical imaging studies that show that white matter pathology in the form of hyperintensities correlates with cognitive decline. We are currently investigating to what degree white matter inflammation results in demyelination, and we will also examine the role of amyloid and vascular pathology in our animal model.

3-C-84 Amyloid-β induced insulin resistance leads to diabetes and aggravated neurodegeneration in transgenic mice

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Alzheimer's Disease (AD) and type 2 diabetes (T2D) increases the risk of each other. Amyloid-β (Aβ) may mediate insulin resistance by competing for insulin binding to its receptor. Insulin is a vital regulator of synaptic function. To examine the impact of T2D on AD pathogenesis, we crossed transgenic mice with pancreatic β-cell specific expression of human islet amyloid polypeptide (hIAPP) to an AD mouse model expressing human amyloid precursor with Swedish (KM670/671/NL) and Indiana (V717F) mutations (APP). APP and double transgenic (DTG) mice showed peripheral insulin resistance. APP mice were hyperinsulinaemic as a compensatory mechanism to maintain normoglycemia. In contrast, DTG mice were hyperglycemic and glucose intolerant. They had increased islet amyloid and Aβ deposition and

reduced β-cell area compared to hIAPP mice, contributing to the exacerbated diabetic phenotype. DTG mice had greater Aβ deposition and hyperphosphorylated tau and reduced immunostaining for synaptophysin, GSK3β phosphorylation and learning and memory compared to APP mice. Insulin levels in DTG hippocampi were significantly reduced. Although a similar reduction in insulin was observed in hIAPP hippocampi, all other parameters remained unchanged compared to non-transgenic controls. This data establishes a role of Aβ in T2D pathogenesis. While a reduction in brain insulin levels appear to have no direct impact on normal brain function, this may lead to aggravation of synaptic dysfunction and cognitive impairment when predisposed to AD.

3-C-85 Reopening the critical period for recovery by augmenting spinal plasticity after cortical stroke

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Significant adaptive plasticity occurs in the spinal cord after a cortical stroke. Notably, this spinal plasticity has a finite temporal window that closes concurrent with a plateau in recovery and reduced efficacy of rehabilitation. Here, we used targeted pharmacotherapy of the spinal cord during the chronic phase of stroke to determine if restarting spinal plasticity can restart recovery. To augment spinal plasticity, adult male Sprague-Dawley rats received intraspinal injections of Chondroitinase ABC (ChABC) into the cervical spinal cord one month after a photothombosis lesioning the forelimb sensorimotor cortex (FLSMC). Rats were divided into groups that received no rehabilitation or reaching rehabilitation of varying intensity. Skilled reaching performance, forelimb use preference, and the distribution of axonal terminals arising from corticospinal tract (CST) projections originating in the spared FLSMC were assessed. We found that ChABC spinal injection significantly increased the number and distribution of ipsilesional CST fibres innervating the spinal cord. Our behavioural data show that ChABC injection improved forelimb recovery after delayed intraspinal administration relative to control. Moreover, ChABC potentiated skilled reaching rehabilitation initiated before or after spinal injection, inducing further recovery at a time point when rehabilitation is inefficient without spinal therapy. These data suggest that augmenting plasticity of the CST long after cortical stroke has occurred improves recovery and rehabilitation from cortical stroke.

3-C-86 Changes in behaviour and resting state functional connectivity in a primate model of Alzheimer's Disease

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Alzheimer's disease (AD) is a devastating neurodegenerative disease and there is an urgent need to develop new therapeutics. Promising drugs developed in rodents have failed to work in AD patients in clinical trials. To bridge this translational gap, our laboratory has developed a non-human primate (NHP) model of AD via intracerebroventricular injection of neurotoxic amyloid beta oligomers (AβOs). This model recapitulates the molecular aspects of human AD pathology, such as tau hyperphosphorylation coupled with tangle formation, synaptic loss, and astrocytic activation. Here, we present preliminary data showing that male rhesus macaques injected with AβOs present with a number of behavioural deficits. Using the cage-side CANTAB apparatus, we observed spatial working memory deficits on the self-ordered spatial search task, and the inability to learn new tasks following AβO injections. In addition

to learning and memory deficits, overall home-cage activity is diminished in injected animals as assessed using 24/7 activity and video monitoring. Finally, resting-state functional connectivity across multiple ROIs between the two hemispheres was observed to be reduced following injections.

3-C-87 Long-term amelioration of seizure-induced hypoxia: Effect on epileptogenesis and behavioural disturbances

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We recently determined that following cessation of brief seizures, a long-lasting, severe hypoxic event occurs in the brain regions involved in the seizure. Previous research has demonstrated that repeated hippocampal seizures in rodents results in severe deficits in hippocampal-dependent memory tasks. However, the contribution of the hypoxic periods that follow seizures on these tasks has not been determined. We hypothesized that rats who received 20-25 seizures but with little hypoxia (via pre-administration of acetaminophen) would not have deficits in hippocampal-dependent tasks relative to those that had seizures with ensuing hypoxia. We also hypothesized that prevention of seizure-induced hypoxia would slow the epileptogenic process in these animals. To test this we used the electrical kindling model to induce seizures in the ventral hippocampus while simultaneously recording oxygen levels in the dorsal hippocampus of adult male Long-Evans rats. Seizures were elicited daily until 20 post-ictal severe hypoxic events occurred. 24 hours following the final kindling session, behavioural testing was initiated (object/context mismatch and Morris water task). We report a significant deficit in spatial and object/context memory in rats subjected to repeated seizures with severe hypoxia. This deficit is ameliorated in rats pre-treated before each seizure with acetaminophen in order to prevent severe hypoxia. We also found that acetaminophen-treated rats had a significantly slower rate of epileptogenesis, as shown by less severe seizures towards the final days of the experiment.

3-C-88 Indications of impaired cerebrovascular buffering of rapid blood pressure changes following one season of participation in contact sports

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The cerebrovasculature behaves as a high-pass filter; high frequency blood pressure (BP) oscillations (>0.20 Hz) are linearly transferred to the brain, while lower frequencies are buffered [1]. It is unknown to what extent the BP-cerebral blood flow relationship is affected by repetitive sub-concussive head trauma. Pre-season testing of two elite hockey and football teams was completed. Non-concussed athletes (n=41) were tested again following the athletic season. BP oscillations were driven by 5-minute repetitive stand-squat manoeuvres at both 0.05 and 0.10 Hz [2]. BP was measured using finger photoplethysmography, while transcranial Doppler was used to measure cerebral blood velocity in the middle (MCA) and posterior cerebral arteries (PCA) Transfer function analysis characterized the coherence (correlation metric), phase (timing offset), and normalized gain (amplitude modulation) between BP and cerebral blood velocity. Paired t-tests indicated coherence and phase offsets were not different from pre- to post-season at either frequency. However, at 0.10 Hz, normalized gain was significantly increased at post-season in both the MCA (%2B42%, $p < 0.001$) and PCA (%2B40%, $p = 0.002$). The observed increases in gain suggest a shift in the high-pass filter behaviour of the cerebrovasculature towards a lower cut-off frequency, rendering the brain more vulnerable to rapid BP

changes. This is a key finding, and raises additional concern over the effects of repetitive head trauma, even at low severities. [1] Zhang et al. (1998) Am J Physiol; [2] Smirl et al. (2015) J Appl Physiol

3-C-89 MRI-guided focused ultrasound-mediated delivery of shRNA targeting α-synuclein in a mouse model of Parkinson's disease

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Parkinson's disease (PD) is a neurodegenerative disorder characterized pathologically by intraneuronal inclusions containing deposits of α-synuclein (α-syn) protein. Selective targeting of α-syn in affected brain regions has significant therapeutic potential as a neuroprotective intervention in PD. However, noninvasive drug delivery to specific brain regions presents a significant barrier to the treatment of PD. Transcranial MRI-guided focused ultrasound (MRIgFUS) combined with microbubbles injected into the bloodstream can locally and transiently increase the permeability of the blood-brain barrier (BBB). Using this approach, systemically administered therapeutics efficiently cross the BBB without invasive surgery. Here, we used a virally expressed short hairpin RNA (shRNA) targeting α-syn to knockdown α-syn gene expression in a transgenic mouse model of PD. MRIgFUS was targeted to the olfactory bulb and dorsal motor nucleus of the vagus. Following targeted delivery of the shRNA, we quantified α-syn expression levels using immunohistochemistry to evaluate the efficacy of viral-mediated α-syn knockdown. We found decreased α-syn immunoreactivity in MRIgFUS-targeted brain regions in comparison to control virus treated mice. Our results demonstrate that MRIgFUS can effectively deliver shRNA targeting α-syn directly into brain areas that are particularly vulnerable to pathogenesis. In addition, FUS-mediated BBB opening in the olfactory bulb and dorsal motor nucleus were effectively targeted for the first time in this study.

3-C-90 Electrophysiological investigation in neurons derived from human induced pluripotent stem cells with disruptions of SHANK2

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Autism is an early onset neurodevelopmental disorder. The pathogenesis of autism is complex, but genetic factors are thought to be critically important in its occurrence. Recent studies report that rare SHANK2 mutations can be involved in Autism Spectrum Disorder (ASD). However, the cellular mechanism(s) by which SHANK2 mutations leads to ASD is poorly understood. We used fibroblast cells from a research subject with ASD with a SHANK2 point mutation (R841X) and established human induced-pluripotent stem cells (iPSCs) in order to determine the electrophysiological characteristics. Whole-cell patch-clamp recordings showed that these cells had properties of functional neurons, displaying action potentials and/or spontaneous excitatory postsynaptic currents (sEPSCs). There were no significant differences in intrinsic membrane properties between the lines from the ASD patient and unaffected controls (parents of the patient and two unrelated individuals). However, statistical analysis revealed an increase in the frequency of sEPSCs in iPSC-derived neurons from the patient with the SHANK2 point mutation, compared with the unaffected controls (1.1 ± 0.2 Hz versus 0.3 ± 0.06 Hz, n=60 each; $P<0.05$). Furthermore, in iPSC-derived neurons from a patient with SHANK2 deletion sEPSC

frequency was also found to be increased, compared with the unaffected controls. Together, these findings suggest causality between SHANK2 disruption and dysfunctional neuronal networks, a synaptic phenotype that may be relevant to altered cognition and sensory perception in autism.

3-C-91 Investigating the effects of Amyloid-beta GxxxG-motif-targeting agents on Abeta42-induced toxicity in a D. melanogaster model

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Alzheimer disease (AD) is one of the most widespread neurodegenerative disorders in the world. Our lab has previously contributed much to the understanding of the amyloid beta 1-42 (Aβ42) peptide as the primary perpetrator in the pathogenesis of AD. We have focused our recent efforts on elucidating the mechanisms of Aβ42 peptide generation, and have discovered a GxxxG interaction motif which seems to be a key region in influencing the aggregation and toxicity of Aβ42 peptides, and represents a novel and promising therapeutic target for the treatment of AD. We now aim to test whether candidate GxxxG-motif-targeting agents can potentially modify the aggregation dynamics and toxicity of Aβ42 to prevent disease in vivo. We established a transgenic Drosophila melanogaster model using the UAS/Gal4 system with eye- or neuron-specific promotors, which allowed us to control the specific expression of human Aβ42 via simple temperature alterations. Eye-specific Aβ42 expression lead to widespread eye degeneration as well as a moderate decreases in survival and locomotor activity of the animals, while neuron-specific Aβ42 expression had no effect on eye morphology but significantly decreased both survival and locomotor activity. Aβ42 levels in the animals were verified using Western blot and correlated with both activities. We will further assess the behavioural and morphological effects of Aβ42 expression using these novel model systems, and subsequently test the efficacy of selected GxxxG-motif-agents in rescuing the Aβ42 induced toxic phenotypes via food supplementation studies.

D – Sensory and Motor Systems

3-D-92 rTMS to the OFA shows increased correlation to right and left FFA

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Functional magnetic resonance imaging (fMRI) shows that brain areas such as the fusiform face area (FFA), the superior temporal sulcus (STS), and the occipital face area (OFA) form a network of key face processing regions. We sought to measure the level of functional synchrony within and across hemispheres in the face network. We measured the effect of repetitive transcranial magnetic stimulation (rTMS) to the right OFA on BOLD signal within the face network using a consecutive TMS-fMRI paradigm. Participants underwent 20 min-1Hz rTMS followed by an fMR-adaptation paradigm. In separate sessions in counterbalanced order, rTMS was delivered in three different conditions: 1) rTMS to the right OFA, 2) sham rTMS, and 3) the control region, right lateral occipital area (LO). rTMS was immediately followed by a face-adaptation fMRI task to measure its effects on BOLD signal. Prior to the rTMS sessions participants underwent two functional localizers in order to extract individual face-processing regions-of-interest (ROIs). Individual Pearson's Correlation Coefficient (PCC) matrices were constructed across ROIs in the different TMS conditions. There was a general increase in the correlation between FFA and OFA BOLD signal in the right and left hemispheres after rTMS to the right OFA compared to sham and TMS to LO conditions. TMS to the OFA reduced BOLD signal, which correlated

with a reduction in BOLD signal in the left OFA and bilateral FFA. These results are consistent with previous findings showing that TMS to the OFA has remote effects in the FFA within and across hemispheres.

3-D-93 Altered structural connectivity associated with visual hallucinations following occipital stroke

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Persistent visual hallucinations following visual pathway damage arise from cell death and disruptions to neural activity. We sought to determine if structural changes in connectivity following damage play a role in visual hallucinations. Diffusion tensor imaging (DTI) was assessed in a patient suffering continuous visual hallucinations for more than 2 years following occipital cortex stroke. Probabilistic tractography was used to delineate the optic radiations. Tracts were further generated from a seed placed at the primary visual cortex (V1) to assess intra and interhemispheric connectivity within the visual cortex and to the temporal lobe. Mean fractional anisotropy (FA) of major white matter tracts were determined. Results were compared to healthy controls. The terminal fibres of the patient's ipsilesional optic radiations were markedly displaced anterior to the lesion site. Reconstructed fibre tracts from V1 in the patient showed an absence of interhemispheric connections from ipsilesional to contralesional V1. Moreover, the ipsilesional tracts in the patient from V1 to middle temporal gyrus were displaced. Congruent with these findings, FA was significantly lower in the ipsilesional inferior longitudinal fasciculus, superior longitudinal fasciculus and cingulum compared to controls ($p < .05$). Cortical remapping and the loss of interhemispheric communication of visual cortices in this patient is consistent with our previous findings showing imbalanced functional activity and recruitment of non-task related regions associated with visual hallucinations.

3-D-94 Cannabinoid type 2 receptors modulate visual information in the primary visual cortex.

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Cannabinoid receptors (CBRs) are present at every level of the visual system, from the retina to the visual cortex. However, the functional role of this system remains elusive. Recently, using immunohistochemistry, we found that CB2Rs are present in layer 5 pyramidal neurons of the primary visual cortex (V1). Therefore, the aim of this study was to determine the functional impact of CB2Rs on neural properties of V1 in mice. Intrinsic and voltage-sensitive dye optical imaging were performed on CB2R KO and WT mice. Retinotopic organization, contrast sensitivity and spatial frequency selectivity (SF) were analyzed. The function of CB2Rs was also assessed using extracellular electrophysiology recordings. Finally, JWH 133 (selective CB2R agonist) and AM 630 (inverse agonist) were administered directly on the cortex to study their local and acute action. When compared to WT, visually-driven optical imaging responses were significantly reduced in CB2R KO mice. Similar effects were seen using the CB2R inverse agonist AM630 in WT mice. On the contrary, CB2Rs activation with JWH 133 caused a strong increase in visual responses. Electrophysiology recordings indicated that CB2Rs activation increased both baseline and stimulation-dependent neuronal firing rates. Our results suggest that CB2Rs play an important modulatory role in neural processes taking place in V1. Anatomical localization and

functional experiments indicate that these effects likely result from a mechanism of action initiated by CB2Rs present in layer 5 pyramidal neurons of V1.

3-D-95 Genetic identification of pain circuits using developmentally regulated Cre expression

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Pain alerts animals to potential and on-going tissue damage. Sensing painful stimuli, termed nociception, originates at sensory neurons which relay pain signals to spinal dorsal horn circuits capable of inducing reflexive behaviours such as limb withdrawal. To elicit more complex behaviours and systemic responses, spinofugal projection neurons (SPNs) relay nociceptive signals to many brain structures, including the medial and ventroposteriolateral thalamus, peri-aqueductal gray and the parabrachial nucleus. These projection pathways remain poorly understood due to a lack of molecular handles whereby they could be manipulated. To uncover novel biomarkers of spinal neurons, including projection neurons, we studied adult transgenic mice expressing Cre in developing spinal cord neurons. Both Math1:Cre and Isl1:Cre mouse strains containing a Cre expression reporter were injected with retrograde tracer dyes into the above pain-related brain areas, allowing us to monitor the presence of Cre in projection neurons. We show that Math1:Cre and Isl1:Cre label a large population of deep dorsal horn neurons, but fail to label significant numbers of SPNs. However, we demonstrate that spinal trigeminal and parabrachial nucleus neurons that innervate the VP thalamus express Math1:Cre. Also, we find that central amygdalar neurons innervating the parabrachial nucleus express Isl1:Cre. These findings uncover a genetic diversity of projection neurons linking various nociceptive centres, allowing us to begin addressing their functional roles with molecular-level precision.

3-D-96 Central Pattern Generator modelling for swimming activity in Zebrafish larva spinal cord

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Locomotion (e.g. walking, swimming) is one of the most basic and important tasks executed by the spinal cord. Locomotor control is thought to arise from a finely organized neural network within the spinal cord that integrates both the motor commands of the brain and sensory feedback to produce the necessary rhythmic motor activity. This dedicated network of neurons, named Central Pattern Generator (CPG), produces both the rhythm and the pattern of muscle contraction necessary to locomotion. Currently, the mechanisms of operation of this network are still poorly understood across vertebrate species. Critical to understanding how locomotion is controlled is how rhythm arises from the neuronal activity of the CPG. Zebrafish exhibit swimming maneuvers at early embryonic stage. Only four different types of spinal neurons are consistently active at this stage (Mn, VeLD/V2b, CoPA/V0v and IC) and all of them are believed to be involved in locomotion. We sought to determine how swimming activity could be generated by a network of these four cells. Using NEURON programming environment, we modeled different patterns of connectivity between the four types of spinal neurons and analyzed the resulting motor output. We tested both chain-like and kernel organization of the IC neurons and our results suggests that a hybrid organization may be found in the embryonic CPG.

3-D-97 Time Course Of Change In Reaches And Proprioception: After Reaching With A Misaligned Cursor

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Training to reach with rotated visual feedback results in adaptation of these hand movements during training, which persists when the perturbation is removed (reach aftereffects). These motor changes also lead to changes in felt hand position, which we refer to as proprioceptive recalibration. The rate by which motor and proprioceptive changes arise throughout training is unknown. Here, we aim to determine the timescale of these changes and their relationship in order to gain insight into the processes that may be involved in learning. We measured reach aftereffects (no-cursor reaches) and perceived hand position after every 6 reach-training trials with a 30° rotated-cursor to 3 radially located targets. To assess proprioceptive recalibration, the right adapted hand was passively moved to one of the three target sites by a robot, and its perceived location was indicated by the left untrained hand. Participants trained with an opposing rotation a week apart to determine if the original training led to any retention or interference of these motor and sensory changes. Results suggest that both motor and proprioceptive recalibration occurred simultaneously and in as few as 6 rotated-cursor training trials (7.57° & 3.88° respectively). Moreover, there was no retention or interference present one week after training. These results suggest that a mere sensory discrepancy may be producing these systematic changes, and emphasizes the unappreciated role that sensory signals play in motor adaptation.

3-D-98 Spatial codes in the superior colliculus delay activity during memory-guided gaze task

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Previously it has been shown that during a direct memory-guided gaze task (variable delay 400-600ms) in head-unrestrained conditions visual and motor bursts in the monkey superior colliculus (SC) encode target location and final gaze position (in eye-centered coordinates), respectively (Sadeh et al., EJN 2015). However, the spatial code during the delay period and its relationship with visual and motor bursts have not been much explored. Here, we fit neural data from 47 delay-responsive SC neurons - 17 visual (V) and 30 visuomotor (VM) - to a series of spatial models created based on a continuum of intermediary positions spanning target (T) and final gaze (G) positions. At the population level, the spatial code in the delay period was described by intermediate models between T and G. For V neurons which mainly showed activity during visual and early-delay epochs, the early-delay code was shifted towards G relative to the visual code. For VM cells (which often showed activity at all epochs) a progressive transition in spatial code from T to G was observed as activity progressed through visual, early-delay, late-delay, and motor epochs. These results show that irrespective of whether or not the neuron exhibited motor burst, as activity evolved through time the spatial code progressively changed from one describing target position towards one determining final gaze position. Similar observations have previously been made in the FEF (Sajad et al., SfN 2015) which, together with these results point to the notion of gradually degrading memory representations in working memory.

3-D-99 Altered Laminar Processing in Multisensory and Auditory Cortical Areas Following Adult-Onset Noise-Induced Hearing Loss

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Hearing loss results in an increased responsiveness of neurons in the auditory cortex to visual stimuli (i.e., crossmodal plasticity). Our recent work has demonstrated that the extrastriate visual cortex, an

area known to integrate audiovisual stimuli, also undergoes crossmodal plasticity following partial hearing loss. Here, we investigated the effect of noise-induced hearing loss on laminar processing in multisensory and auditory cortical areas. Adult male rats underwent baseline hearing testing, followed by a bilateral noise exposure. Two weeks later, acute electrophysiological recordings were performed by inserting a multichannel electrode array perpendicular to the cortical surface so as to record across all cortical layers simultaneously in the lateral extrastriate visual cortex (V2L), and the dorsal auditory cortex (AuD). For each penetration, computer-generated auditory, visual and combined stimuli were delivered, and responses were compared to age-matched controls. A current source density analysis showed increased sink amplitudes to visual stimuli and decreased sink amplitude to auditory and audiovisual stimuli across the cortical layers in V2L. Conversely, following noise exposure, AuD showed increased sink amplitudes in only the granular layer to auditory and audiovisual stimuli. Thus, the degree and nature of crossmodal plasticity differed across neighboring cortical areas; V2L showed a decrease in auditory input across all cortical layers, whereas AuD showed increased auditory input in the granular layer following adult-onset noise-induced hearing loss.

3-D-100 Audiovisual Temporal Processing in Rats as Assessed by Novel Operant Conditioning Tasks

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In providing us with a more complete sensory experience, our brains naturally merge information from our different senses. Consequently, humans are capable of precisely judging whether auditory and visual stimuli are presented at the same (synchronous) or different (asynchronous) moments in time. That said, for each person, there exists a temporal binding window in which auditory and visual stimuli that are presented at nearly the same time (e.g., offset by ~40 ms) are actually incorrectly perceived as occurring simultaneously. In this study, we endeavored to design the first behavioural task capable of assessing the temporal binding window in rats, as such a model would then allow for electrophysiological investigation into the neural basis of audiovisual temporal integration. To that end, we developed both a go/no-go task as well as a two-alternative forced choice task in which rats were trained to accurately discriminate (>80%) between audiovisual stimuli presented synchronously (i.e., 0 ms offset) or asynchronously (i.e., visual preceding auditory stimulus by 200 ms). On test days, ambiguous trials (10-100 ms offset) were presented to determine each rat's temporal binding window. Largely consistent with studies on humans, both tasks revealed a sigmoid relationship between stimuli offsets and performance accuracy, such that ~50% of trials presented at a 40 ms offset were incorrectly perceived as being synchronous. Future studies will use our novel behavioural tasks to study compromised audiovisual temporal integration in preclinical rat models.

3-D-101 A pixel-computable stabilized supralinear network model of V1

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No model of V1 to date has captured all observed response phenomena. Linear kernel methods with threshold and divisive non-linearities can reproduce classical receptive field behaviour, but not the full range of non-classical behaviours. The stabilized supralinear network, or SSN (Rubin, Hooser & Miller, 2015, Neuron) provides a simple scheme of lateral interactions that produce a wealth of observed V1 behaviour not previously captured with linear kernel methods. However, the SSN is restricted in

stimulus selectivity and is not pixel-computable, but rather requires an arbitrary orientation-dependent activation function as input. It is not yet clear how the SSN interacts with mechanisms through which such inputs arise. By integrating a linear kernel model with the SSN we produced a model that is pixel-computable and produces a wide range of classical and non-classical behaviour. We also expanded the SSN to use binocular stimuli. Using an optimization procedure, SSN parameters were found that realistically reproduce interocular transfer of suppression in excitatory units, but not inhibitory ones. This work is a step toward a more comprehensive account of V1 responses.

3-D-102 Challenging the Labeled Line Theory: Itch and Pain can be Coded by a Single Afferent Population

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Itch, or pruritus, is an unpleasant sensation that leads to scratching behavior or the desire to scratch. Despite significant structural and behavioral overlap of pruriception and nociception, the underlying neurophysiological basis of itch sensation and its relation to pain remains unclear. There have been several theories proposed for the discrimination process of itch and pain by the somatosensory system. One of the most popular ones is the "labeled line" theory which claims that dedicated components of the somatosensory system, from the periphery to the brain, are specifically specialized for detection, transmission and perception of each sensory modality. To examine this theory we have designed experiments by taking advantage of chemogenetic and optogenetic approaches. We targeted the chemogenetic actuator hM3D and the optical actuator ChR2 selectively to the MrgprA3(chloroquine receptor)-positive subpopulation of C-fibers known to be specifically linked to itch (Han et al., 2013). Using the cheek model of itch (Shimada and LaMotte, 2008), we observed that injection of hM3D ligand, evokes stereotypical itch behavior rather than pain responses. Surprisingly, optical activation of these neurons through ChR2 predominantly induced pain avoidance behaviors rather than scratching. Our results dispute the "labeled line theory" and show that in vivo a single population of C-fibers is capable to convey itch sensation in certain stimulation conditions and pain sensation in others.

3-D-103 Von Economo neurons in Indian green Ring neck Parrot (Psittacula krameri): possible role in vocal learning

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In this study we report the existence and localization of a rare, large spindle shaped neuronal type, known as the von Economo neuron (VENs) in Indian parrot; those have not been observed in any other bird species to date. This study is the first preliminary report of avian VENs. Originally these neurons were found in III and V layer of anterior cingulate cortex (ACC), fronto- insular cortex (FI), and dorso-lateral prefrontal cortex (DLPFC) of humans and some distantly related group of mammals and correlated with higher level of consciousness, intuition, social awareness and regulation of homeostasis, on the basis of their location in human brain. The VENs appear to be fast-projection neurons, although their targets are still not incontrovertibly known in different mammals. We encountered such type of neurons in bird species which do not have neocortex. In parrot, these neurons were situated mainly in medio-lateral pallial region, the nidopallium caudo- lateral (NCL), Arcopallium (A), and dorso-lateral corticoid (CDL) area of telencephalon. We compared location, detailed morphometry and architecture of Nissl and Golgi impregnated VENs with mammalian VENs to illuminate their resemblance. Presence of

VENs in parrots may be related to their behavioral specializations common to hominids, whales, and elephants like vocal learning, emotion and social behavior. The presence of VENs in Psittaciformes birds provides new insight to understand their behavioral specializations in different animals, and their possible role in vocal production learning.

3-D-104 Deactivation of PMd and A5 in non-human primates impairs corrective responses to mechanical disturbances of the limb

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Recent studies highlight that neural responses to mechanical disturbances of the limb is quickly transmitted throughout sensory and motor cortices in non-human primates. However, the causal functions of these areas in the generation of the corrective response remain unclear. Here we investigated the contribution of dorsal part of premotor cortex (PMd) and parietal area 5 (A5) to feedback control of the upper limb by deactivating these areas with a reversible cortical cooling technique. We trained a male rhesus monkey to perform a unilateral arm postural control task. While the monkey maintained the finger tip in a circular target (0.8 cm radius), a mechanical step-torque perturbation was applied and the monkey was required to return to the target in 500 ms. During the task, we cooled the PMd or A5 with chronically implanted probes (cryoloops). We quantified the speed ('return time') and accuracy ('endpoint error') of the corrective response before, during and after cooling. Results showed that the PMd cooling increased both return time and the endpoint error relative to the control condition (sham cooling), suggesting that the PMd cooling affected the response gain for the perturbation. On the other hand, the A5 cooling increased the endpoint error, but did not change the return time, suggesting that the A5 cooling affected the estimation of the limb or target position. These results indicated that these areas have unique contributions to the feedback control of voluntary limb movements.

3-D-105 Sciatic Nerve Exposure to Non-Compressive Nucleus Puplosus Elicits an Acute Inflammatory Neuritis Mediated by Neurotrophin Expression

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Objective Disc-herniation induced radiculopathy arises from both compression and inflammation of apposed nerves. The mechanisms that underlie painful neuropathy remain undefined. We demonstrated the effect of nucleus pulposus (NP) on inflammatory activation which requires intraneural macrophage migration to generate painful neuropathy. Methods Mouse peritoneal macrophages were cultured in NP-conditioned media. Neurotrophin expression was measured by PCR and Nitric Oxide (NO) measured by the Griess test. C57BL/6 mice underwent surgery to implant littermate tail NP on the sciatic nerve. Mechanical and thermal thresholds and gait were assessed for one week post-surgery. Macrophage infiltration was assessed by immunohistochemistry. Results Peritoneal macrophages exposed to NP-conditioned medium for 72 hours show increased NO and neurotrophin expression. NP mice developed mechanical, cold and thermal hypersensitivity. Macrophage infiltration and autoreactive lymphocytes were observed. Macrophage depletion prevented pain behaviours. Knocking out neurotrophin activity permitted perinenural macrophage accumulation but eliminated intraneural macrophage migration and pain behaviours. Conclusion Disc NP induces inflammatory activation among macrophages as well as upregulated neurotrophin expression. The disc herniation model leads to pain

behaviour that requires intraneural macrophage migration. Strategies to decrease perineural inflammation or maintain integrity of the blood nerve barrier may be effective in treating painful disc-herniation radiculopathy.

3-D-106 Peripheral Hypersensitivity to Subthreshold Stimuli Persists after Resolution of Acute Experimental Disc-Herniation Neuropathy

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Objective While acute disc-herniation-induced radiculopathy most frequently resolves without clinical sequelae, a fraction of patients will experience long-term sensory or motor dysfunction. This study examined the chronic sensitivity of the rodent hindpaw after resolution of acute inflammatory neuropathy. Methods C57BL/6 mice underwent implantation of littermate tail nucleus pulposus (NP) onto the sciatic nerve. Animals were tested for mechanical and cold allodynia, thermal hyperalgesia, and gait three weeks post-surgery until the acute phenotype resolved. Mice were then injected with intraplantar subthreshold capsaicin or vehicle, and were assessed by the same behavioral testing. Dorsal root ganglia (DRG) were studied by PCR and immunohistochemistry for cation channel expression and explants were assessed ex vivo for capsaicin sensitivity to cation-channel activation using cobalt staining. Results Mice exposed to NP demonstrated pain behaviors including mechanical allodynia, increased cold and heat sensitivity, and RotaRod imbalance after subthreshold capsaicin. DRG derived from NP-treated animals showed greater cobalt staining in response to capsaicin. Conclusion Non-compressive disc herniation leads to altered long-term sensitivity in the sciatic nerve territory. This sensitivity persists despite resolution of acute intraneural macrophage migration. The heightened expression and function of cation-channels in sensory neurons may represent a mechanism by which acute inflammatory pain transforms into chronic neuropathic pain.

3-D-107 Goal-dependent modulation of the long-latency stretch response accounts for orientation of the arm

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We recently had participants complete goal-directed reaches following mechanical elbow perturbations that displaced the hand towards or away from a target. Perturbations that displaced the hand away from the target increased the long-latency stretch response (muscle activity 50-100 ms following a perturbation: LLSR) from the stretched elbow muscle as well as from the wrist muscle that assisted in moving the hand to the target. This coordinated goal-dependent modulation across multiple muscles suggests that sensory information is rapidly used to support the demands of the intended goal-directed action. Here, we tested whether the LLSR of wrist muscles would reflect the orientation of the arm in the horizontal plane (i.e., thumb up: TU; or thumb down: TD). Positive results would indicate that the rapid processing of sensory information accounts for configuration of the body relative to the movement goal. Participants reached to targets in both arm orientations following elbow perturbations that moved their hand into or away from the target. Notably, TU or TD orientations governed the wrist muscle that assisted moving the hand to the target. We found that flexion perturbations that moved the hand away from the target resulted in large LLSR from wrist extensor and wrist flexor muscles when the arm was in the TU and TD orientation, respectively. The opposite pattern was observed for extension

perturbations that moved the hand away from the target. These findings provide further evidence of the rapid and flexible use of sensory information to support goal-directed actions.

3-D-108 Pannexin Channel Expression and Function in the Olfactory System of a Knock Out Panx1 Mouse Model

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Pannexins (Panx) are ubiquitously expressed transmembrane channels that are capable of conducting large molecules upon activation. Panx1 is the most extensively investigated member of the protein family, having implications in sensory perception based on its ability to release ATP and modulate purinergic signaling. The discovery of Panx1 expression in the olfactory epithelium (OE) raises the question whether Panx1 mediates ATP release responsible for modulating chemosensory function. Here, we investigated the specific localization and function of Panx1 in the OE using a Panx1 knock out (KO) mouse line. We demonstrated a novel localization of Panx1 to the axon bundles of the olfactory sensory neurons (OSNs) using immunohistochemistry (IHC). The functional analysis in vivo suggested that Panx1 is dispensable in olfaction. However, a challenge emerging from KO mouse models is the question of compensatory upregulation of other Panxs. Using qPCR, we found upregulation of Panx3 in Panx1 KO mice. With IHC, we have compared the expression patterns of Panx1, 2 and 3 in the primary accessory olfactory organ, the vomeronasal organ (VNO), and have discovered a specific upregulation of Panx3 in the basal sensory epithelial layer of the VNO in the Panx1 KO population. This result is consistent with a recent report on the upregulation of Panx3 in the arterial walls and skin of Panx1 KO mice, suggesting that Panx3 could be compensating for the functional properties of Panx1 in chemosensory processing.

3-D-109 DTI reveals asymmetry in the optic radiations following early monocular enucleation

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Early monocular enucleation results in enhanced visual spatial processing and better sound localisation. These behavioural findings are supported by neuroimaging studies that demonstrate morphological changes, including decreased lateral geniculate nuclei (LGN) volumes, and increased surface area and gyrification in visual, auditory and multisensory cortices. Given these differences in people with one eye we investigated how the loss of one eye affects the development of connectivity within the visual system. Participants were scanned using diffusion tensor imaging (DTI) and probabilistic tractography was performed to delineate the optic radiations. Seeds were placed at the LGN with waypoints and termination points in primary visual cortex. Tract-based spatial statistics were used to extract the skeletonised fractional anisotropy (FA) values of the reconstructed optic radiations. Mean FA values were compared between individuals who had undergone early monocular enucleation and controls. Unlike controls, people with one eye exhibited a hemispheric asymmetry, with significantly larger FA values in the right optic radiation compared to the left, independent of eye of enucleation. The asymmetry suggests structural changes to the optic radiations in people with one eye. This difference in FA may reflect compensatory changes in the right hemisphere in order to preserve normal function, however, it may also be the result of a deficit in a left lateralised function. Overall, this asymmetry could indicate accommodation for the loss of an eye early in life.

3-D-110 HD-tDCS over the mIPS affects movement planning

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The medial part of the intraparietal sulcus (mIPS) is thought to play a critical role in the integration of target- and effector-related information during reach planning and yet its precise functional contribution remains unclear. Here we used high definition-transcranial direct current stimulation (HD-tDCS) to locally modulate neuronal excitability in a polarity-specific manner in the left mIPS during visually-guided reaching. Left mIPS was independently identified in each participant (N = 8) with functional MRI based on its selectivity to pointing versus saccadic eye movements and we used neuronavigation to administer anodal and cathodal stimulation (2mA for 20min; 3cm radius 4x1 electrode placement) in two separate testing sessions (order of stimulation was counterbalanced across participants). During testing, participants performed memory-guided reaching movements from one of 2 initial hand positions (5cm left/right of midline) to one of 4 briefly flashed targets (20cm distant, 5cm apart horizontally), while maintaining central fixation. Each participant completed a minimum of 200 control, stimulation and post-stimulation trials. In general, cathodal stimulation produced more horizontal and vertical overreaching than anodal stimulation. Further, anodal stimulation resulted in an undershooting of reach targets in the horizontal plane whereas cathodal stimulation resulted in a leftward target bias. These results support a role for mIPS in reach planning and validate the use of HD-tDCS as a tool to study the causal role of cortical areas in movement planning.

3-D-111 Two-stage bimanual coordination learning

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Bimanual activities are crucial in daily life. So far, studies mostly focused on bimanual coordination in simple/rhythmic activities. Our aim is to analyze the early stages of bimanual learning. Using a bimanual manipulandum, 51 healthy individuals (5 groups) participated in a bimanual task. They were instructed to drive a cursor along one of two circuits (C1/C2) as fast & accurately as possible. One hand controlled horizontal displacements, the other the vertical ones; hand motions were constrained in these directions by stiff virtual walls. Two groups of subjects (G1 & G4) were trained on one circuit for 15 min; subjects in G4 were then tested on the other circuit. For G2 & G3, circuits C1/C2 alternated at each trial; subjects in G2 (G3) started with C1 (C2). Finally, G5 participants were trained on C2 for only 5 min and tested on C1 afterwards. Hand kinematics were measured at 1 kHz. We computed a bimanual coordination index and a speed-accuracy trade-off (SAT). Coordination and SAT rapidly improved over the first 5 min and then continued to improve more slowly until the end of training. Alternating the circuits (in G2 & G3) affected the performance more in the later phase than in the first 5 min. In addition, while changing the circuit after 15 min of training (G4) resulted in a large drop of performance, the same change after 5 min of training (G5) did not affect performance significantly. We believe that the first phase reflected predominantly bimanual coordination learning while the later (circuit-specific) phase reflected predominantly motor sequence skill learning.

3-D-112 Cortical movement representations during unimanual and bimanual wrist movements in humans

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There have been lots of neurophysiological evidences not only for contralateral, but also for ipsilateral movement representations during unilateral arm movement. However it is still unclear how these two representations interact to achieve coordinated bimanual movements. Here we address this issue by focusing on the similarity structure of multivariate brain activity patterns while human subjects perform either unimanual or bimanual movements in the fMRI scanner. Seven subjects performed either unimanual or bimanual wrist pointing movements towards one of six visual targets per each hand during the scanning sessions. We calculated the dissimilarity across activation patterns for different movement conditions, and compared it with that predicted from a directional tuning model to examine whether and how wrist movements were represented in certain brain region. Consistent with previous studies, we found strong directional tuning for the contralateral wrist motion around the primary motor cortex (M1), the dorsal premotor cortex (PMd), and intra parietal sulcus (IPS). There were also substantial ipsilateral movement tuning in right M1, PMd, and bilateral IPS as well as bimanual movement tunings in right M1, and bilateral PMd and IPS. Further analyses showed that the tuning pattern in the bilateral IPS is better characterised by multiplicative integration of single hand tuning functions rather than additive integration of them. The results suggest that IPS is key region to nonlinearly integrate bilateral movement information for bimanual coordination.

3-D-113 V3 Spinal Interneurons Are Crucial In Regulating Weight-Loading Movement

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V3 interneurons (INs) are a major group of glutamatergic commissural neurons located in the spinal cord. They innervate motor neurons and many other ventral INs and are essential for producing a robust and organized locomotor rhythm. Until now, however, the mechanisms underlying the function of V3 INs in locomotion is still unclear. To address this question, we have systematically examined the kinematics and muscle activities of hind limbs of a mutant mouse, in which the expression of Vesicular Glutamate Transporter 2 (VGLUT2) is specifically deleted in the V3 INs. We studied the movement of these mutant mice under different conditions, such as walking on a horizontal or an inclined surface at different speeds. We discovered that without V3 INs, the animals couldn't move their hind limbs or position their feet correctly during stance phases, indicating a deficiency in their weight-loading movement. Electromyography (EMG) recordings showed that the activity patterns of flexor and extensor muscles of the mutant mice were different from those of their counterparts in wild-type mice. For example, during walking on inclined surface, the activity of extensor muscles greatly increased in control animals, while there were little changes in these muscles in the V3-VGluT2 mutant mice. The phase relationships of these muscles during stance and swing periods were also different between mutant and wild-type mice. Combined with other in vitro recordings and anatomical studies, these results indicated that V3 neurons might be involved in spinal circuits that provided a sustained excitabi

E – Homeostatic and Neuroendocrine Systems

3-E-114 The GABAergic neurosteroid 3α-androstanediol protects SH-SY5Y human neuroblastoma cells against prolonged ERK phosphorylation induced by hydrogen peroxide and amyloid β peptide

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Neurosteroids influence a large number of neuronal processes. Many reports have suggested that the protective effects of sex steroids against neurodegenerative diseases may be due to conversion to active metabolites, including neurosteroids that modulate neuronal sensitivity to gamma-aminobutyric acid (GABA). 5α-androstane-3α,17β-diol (3α-diol), a metabolite of testosterone, allosterically potentiates the activity of GABA at the GABA-A receptor. Intriguingly, elevated free testosterone levels have been correlated with a reduction in the risk for Alzheimer´s disease. Dysregulation and prolonged phosphorylation of extracellular signal-regulated kinase (ERK) is an indication of cellular toxicity, and has been implicated in amyloid-induced neuronal deficits in Alzheimer´s disease. Therefore, we sought to determine whether 3α-diol could protect against neurotoxic ERK phosphorylation induced by hydrogen peroxide (H2O2) and amyloid β peptide 1-42 (Aβ42) in SH-SY5Y human neuroblastoma cells. In addition, we investigated if 3α-diol influences the physiological phosphorylation of ERK by acetylcholine, via nicotinic cholinerigic receptors. 3α-diol prevented the increase in ERK phosphorylation 24 hours after treatment with H2O2 or Aβ42 treatment, and 48 hours after treatment with Aβ42, without having any effect on the short-term activation of ERK by acetylcholine. This suggests that 3α-diol protects against cellular stress without disrupting normal neuronal ERK signaling, indicating that it may play a role in the prevention of amyloid-induced neurotoxicity.

3-E-115 The role of Growth Hormone as a neurotransmitter involved in depression: A human model

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Learning and memory are thought to be induced by growth hormone (GH) through specific receptors located in areas of the CNS and via excitatory circuits associated with these behaviours (Nyberg and Hallberg, 2013). We used the model of humans exposed to chronically elevated levels of GH (Acromegaly) to determine whether: 1) depression might be more common in patients with excess GH, and, 2) surgery to remove the source of excess GH changed the rate of depression seen in these patients. We collected CES-D questionnaires (score>16/60=depression), sex, age, tumor characteristics on pituitary tumor patients (n=68) at St. Michael's Hospital over a five year period. We divided groups into before surgery(preop) or after surgery (2 groups - up to 6 months post-surgery(post1) or after 6 months post-surgery(post2)). CES-D elevations indicative of depression were seen in 32% of patients preop. This decreased to 13% post1, closer to the Canadian lifetime prevalence of 12% (Langlois et al., 2012). However, it slightly rebounded to 19% post2, following a U-trend. An inverted-U trend was found for age vs. preop CES-D. Although there was no sex difference in CES-D pre-surgery, males did not show as much decrease post-surgery as did females. The acromegalic model was a useful one to explore potential insights into the role of GH in humans. The findings in depression show differential effects based on age and sex and require further study. These observations in humans suggest new avenues for research into the role of GH in neuroscience and in particular, in understanding depression.

3-E-116 The effects of neuropeptide Y on dissociated subfornical organ neurons.

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The subfornical organ (SFO) is a sensory circumventricular organ, lacking a blood-brain barrier. Neurons of the SFO are exposed directly to the ionic environment and circulating signaling molecules, providing a unique window for communication of physiological status from the periphery to the CNS. The SFO is recognized as a key site for hydromineral balance, cardiovascular regulation and energy homeostasis. Neuropeptide Y (NPY) is a potent stimulator of food intake when released a centrally from a subpopulation of arcuate nucleus neurons and has well-documented pressor effects when released peripherally. Given the role in energy balance and cardiovascular function of both NPY and SFO neurons, it is surprising that the effects of NPY on SFO neurons have never been investigated. The aim of this study was to determine whether NPY affects the electrophysiology of SFO neurons. Using whole cell patch clamp techniques on dissociated SFO neurons from Sprague Dawley rats, we report that 100 nM NPY caused approximately one third of SFO neurons to depolarize, one third hyperpolarize and one third no response. The EC50 of the combined effects was 10 nM NPY. Specific NPY receptor antagonists were applied, suggesting opposing effects of the Y1, Y2 and Y5 receptors. We also observed that NPY caused a decrease in the inactivating K+ current as well as the persistent Na+ current, mediating the depolarizing and hyperpolarizing effects, respectively. These findings indicate that NPY elicits electrophysiological changes on SFO neurons, suggesting that the SFO is a key site of action for NPY.

3-E-117 Stress as a contagion: Synaptic imprinting following social interactions in rodents

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Neural changes caused by stress further refine adaptive behaviors necessary for survival. Many social animals, including humans, also adapt their behaviors as a consequence of stress experienced by a conspecific. If animals transmit information about experiences to modify behaviors of conspecifics, then this information should imprint at similar synapses in the stressed and unstressed conspecifics. Here we investigated whether synaptic changes in a stressed mouse "phenocopy" to the same synapses in a naïve cagemate. We focused on an activity-dependent form of synaptic plasticity we have described at glutamate synapses on hypothalamic CRH neurons in mice. One mouse (Crh-IRES-Cre, tdTomato) from a same-sex pair was removed from the cage and either exposed to a stressor (footshock, 0.5 mA for 2 seconds every 30 seconds, 5 minutes) or placed in a separate cage for 5 minutes. The pair was then placed in the homecage for 30 minutes. Both mice were then anaesthetized and coronal brain slices prepared for electrophysiological experiments. 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. Remarkably, conspecific cagemates that were exposed to the stressed mouse, but not the stress itself, exhibited the same synaptic plasticity. Yolked controls showed no short-term plasticity. These observations demonstrate that the impact of acute stress on one animal can manifest as synaptic changes in another animal.

3-E-118 The Tubby protein regulates expression of genes involved in metabolism and neuronal functions

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Obesity is a one of the leading public health crises in Canada. Currently, we do not fully understand the neuronal regulation of metabolism and appetite, and what happens during development of metabolic disorders such as obesity. Rodent models of obesity have aided in advancing our understanding of

metabolism and appetite. One such model is the tubby mouse, which has a mutation in the Tubby (Tub) gene and displays maturity-onset obesity, insulin resistance, and sensorineuronal degeneration. Tub is highly expressed in the hypothalamus and belongs to the Tubby family of proteins which are characterized by a highly conserved C-terminal domain known as the 'Tubby domain'. Structure-functional analyses have suggested that the Tubby domain has nucleic acid binding properties, indicating that Tub might act as a transcription factor. Using a Tub-overexpression system, we have identified that Tub regulates expression of genes involved in appetite regulation, metabolism, neuronal growth and function. One of the genes that Tub regulates is neuropeptide Y (NPY) which is known to play a key role in metabolism and food intake. Our data suggests that Tub either directly or indirectly downregulates the expression of NPY such that very little to no NPY-immunoreactivity is observed in Tub overexpressing cells. These data are consistent with NPY misregulation in tubby mice. To the best of our knowledge, this is the first time Tub has been shown to regulate the expression of NPY. In the future, we hope to elucidate the mechanism behind Tub-dependent downregulation of NPY.

3-E-119 Maternal Circuits that Respond to Mouse Pup Vocalizations: D2 Dopamine and Oxytocin Receptors

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Social communication and bonding are associated with dopamine, oxytocin and prolactin production in many mammalian species (Rilling & Young, 2014). Ultrasonic vocalizations (USVs) in isolated 3-11 day old rodent pups increase maternal behaviors and hormonal responses, including retrieval, nursing, prolactin and oxytocin (Woehr et al., 2010). D2 dopamine receptor gene deletions, for example, reduce maternal responses and prolactin changes to pup vocalizations (Curry et al., 2013). Oxytocin receptor gene deletions reduce maternal responses to pups similarly (Hidema et al., 2015). Oxytocin neuronal projections from paraventricular nucleus to forebrain areas, such as olfactory and auditory cortex, and hippocampal CA2/3, have been associated with social recognition and bonding (Marlin et al., 2015). Maternal responses in rodents depend on the dam's left auditory cortex, where oxytocin receptors improve neuronal sensitivity to pup USVs. Oxytocin and vasopressin receptors on hippocampal CA2 and CA3 pyramidal neurons improve sensitivity to entorhinal cortex inputs relevant to social recognition (Pagani et al., 2015). These CA2/3 pyramidal neurons activate CA1 neurons needed for social memory in male mice (Hitti & Siegelbaum, 2014). Therefore, when dams retrieve and nurse pups after USVs, oxytocin and prolactin production in the hypothalamus may, at the same time, facilitate retrieval, social recognition, bonding and memory via oxytocin neurons that project to mesolimbic, limbic, auditory, olfactory, and CA2/3 hippocampal circuits.

F – Cognition and Behavior

3-F-120 Induction of 50 kHz vocalizations by dopamine and apomorphine from nucleus accumbens and lateral septum

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It has been established that production of 50 kHz calls, associated with appetitive states, involves activity of the ascending mesolimbic dopamine pathway from the ventral tegmental area to the nucleus accumbens (NAcc). However, this pathway innervates multiple forebrain structures beyond the NAcc. To

date, very little research has been done to uncover what other structures are associated with 50 kHz call production beyond this structure. Apomorphine (a broad spectrum dopamine agonist) was unilaterally microinjected (3µg) into both the NAcc shell and the lateral septum (n = 28). Rats emitted a high number of 50 kHz calls in response to apomorphine in either the NAcc shell or the lateral septum compared to vehicle alone. These findings implicate the lateral septum in production of 50 kHz vocalizations and confirm a direct role of dopamine in 50 kHz call production. To examine this role further, 15 rats received 4 different doses of dopamine (15, 30, 60, and 120µg) into the NAcc shell. Results indicated a dose-dependent induction of 50 kHz calls in response to direct microinjections of dopamine. A separate 11 rats received microinjections of dopamine (30µg) into the NAcc shell, core, and the lateral septum. Results showed comparable numbers of 50 kHz calls in lateral septum and NAcc shell induced by dopamine. These findings are strong evidence that not only dopamine plays an important role in 50 kHz call production but that the response can be induced both from the NAcc shell and lateral septum. Further functional mapping should follow. Supported by NSERC

3-F-121 5-HT1A receptor and its transcription factors Freud-1 and Freud-2 in the brain of rats with genetically determined fear-induced aggression or its absence

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Serotonin 5-HT1A receptor plays a crucial role in the mechanisms of genetically defined aggression. In its turn, 5-HT1A receptor functional state is under control of multiple factors. We investigated the expression of 5-HT1A receptor and its transcription factors Freud-1 and Freud-2 in the brain of rats selectively bred for more then 80 generations for either high level of fear-induced aggression or its absence. It was shown that 5-HT1A receptor level was decreased in the midbrain and increased in the hippocampus of highly aggressive rats. These changes were not accompanied by considerable alterations in 5-HT1A receptor gene expression. Nevertheless, levels of Freud-1 and Freud-2 were different in aggressive and nonaggressive rats. Freud-1 level was decreased in the hippocampus, whereas Freud-2 level was increased in the frontal cortex of highly aggressive rats. Decrease in Freud-1 protein level was accompanied by considerable reduction in the expression of the gene encoding Freud-1 in the frontal cortex of aggressive animals. Thus, our data indicate that Freud-1 and Freud-2 are involved in the regulation of fear-induced aggression. It could be suggested that Freud-1 and Freud-2 do not affect transcription of the 5-HT1A receptor gene in the brains of investigated rats. Moreover, obtained data indicate the implication of posttranscriptional rather then transcriptional regulation of 5-HT1A receptor functional state in the mechanisms of genetically determined aggressive behavior. The study was supported by the RSF grant № 14-15-00025.

3-F-123 Evaluating the role of GABA interneurons in the medial prefrontal cortex during working memory in mice

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Working memory involves coordinated timing and synchrony of network activity in the medial prefrontal cortex (mPFC) by GABA interneurons. GABA interneurons are a diverse population with distinct cell types contributing differently to cognition and behaviour. Two major non-overlapping GABA interneuron populations in the mPFC are the parvalbumin (PV)- and cholecystokinin (CCK)- GABA interneurons. We examined the requirement of PV-GABA and CCK-GABA interneurons in working memory by

optogenetically silencing their activity in the mPFC of mice performing an olfactory delayed-nonmatch-to-sample test. The inhibitory opsin ArchT was expressed in CCK-GABA interneurons using dual recombinase intersectional genetic labeling, and in PV-GABA interneurons using AAV-mediated gene delivery. PV-GABA and CCK-GABA interneurons were inhibited either during the sample, delay, or response phase of the task by light illumination timed to these events. CCK-GABA interneuron inhibition selectively during the response phase impaired working memory performance, as indicated by an increased number of false alarm errors. These results support the specific function of CCK-GABA interneurons in the retrieval process of working memory.

3-F-124 Opposite effects of nucleus accumbens shell D1 and D2 receptor antagonism in approach-avoidance conflict resolution

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The nucleus accumbens (NAc) is importantly implicated in the processing of approach and avoidance signals evoked by emotionally valenced environmental stimuli. Currently, there is evidence to suggest that such opposing motivational processes are differentially mediated by subpopulations of NAc neurons expressing either dopaminergic D1- or D2-receptors (D1R, D2R). The role of these neuronal subtypes in mediating approach-avoidance behavior while an animal is in a state of motivational conflict is, however, unknown. The present study utilized a mix-valenced conditioning paradigm to examine the effects of NAc shell D1R or D2R antagonism on approach-avoidance behavior. Male Long Evans rats were trained in a three-arm radial maze to associate visuo-tactile cues with sucrose, shock, or neutral outcomes delivered within the arms in which the cues were presented. Following conditioning, rats were intracerebrally infused with D1R antagonist SCH23390 or D2R antagonist Sulpiride in the NAc shell. 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 mix-valenced arm. We conclude that NAc shell D1R is importantly implicated in eliciting approach behaviors, and NAc shell D2R is important for suppressing approach behaviors, when the valence of the outcome is uncertain.

3-F-125 Correlation between cognitive decline and blood pressure in elderly patients with controlled hypertension

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Introduction Recent studies suggest that the blood pressure (BP) threshold should be reduce to decrease end-organ damages. These facts underscore the urgency to better understand the mechanisms of underlying brain aging acceleration in hypertensive patients. Objective Determine whether BP still correlates with poor cognitive performances when comparing subjects treated and controlled for high blood pressure to untreated normotensive subjects. Methods The 48 recruited subjects aged between 65 and 85 years old, were divided in two groups: "Normotensive (NT)" (n=26) and "Controlled Hypertensive (HT)" (n=22). Subjects were assessed for: a) Systolic blood pressure (SBP) & Diastolic blood pressure (DBP); b) Ambulatory blood pressure monitoring (24 hours); c) Blood analysis (Na%2B, K%2B, Ca%2B%2B, glucose, etc). Participants completed a battery of neuropsychological tests; including the

Trail Making Test parts A and B (TMTA & TMTB) and the Stroop Colour-Word Test (SCWT) with its four conditions. Results The largest difference between groups was on SCWT performance. Significant correlations ($p<0.05$) were found between "% of daily BP>135 mmHg" and the cost of switching (CS-SCWT). In switching conditions (SWC), HT subjects performed worse than NT subjects. SWC assess executive functions deficits, and have been reported as predictors of cognitive decline in older adults. Conclusion There is a strong correlation between the "% of daily BP>135 mmHg" and poor executive functions, reinforcing the hypothesis that the BP threshold should be decreased to protect brain of HT subjects.

3-F-126 fMRI reveals the evolution of representational content during a delayed match-to-sample task

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Several recent findings have revealed medial temporal lobe (MTL) involvement in tasks that do not emphasize mnemonic processing. In particular, perirhinal cortex (PRC) has been implicated in visual discrimination tasks involving complex stimuli such as human faces, even in the absence of long-term declarative memory demands. Currently, little is known about the specialized role ventral visual stream (VVS) and PRC -based representations serve as visual information is perceived, maintained and encoded. Here, we used functional magnetic resonance imaging to examine MTL and VVS responses to individual stimuli in the context of a delayed match-to-sample task designed to address these issues. A study item was presented, and following a delay, participants were presented with a test item, indicating with a button press if this item differed from the study item. Critically, interfering items from a different stimulus category than the target were presented to participants while the target item was being maintained in working memory, creating conflict between the contents of working memory and ongoing perception. This design allowed category evidence to be tracked and compared at each phase across the brain. Our preliminary findings revealed differential contributions of MTL and VVS structures across perception, maintenance, and interference phases. Together, our findings help shed light on the specialized nature of representations in the VVS and MTL, and how these representations support perception as well as working and long-term memory.

3-F-127 Resting-state MEG oscillations predict working memory scores on neuropsychological tests

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Only a handful of studies have focused on the putative relationship between brain oscillations at rest and cognitive performance. Working memory (WM), the ability to manipulate information on items kept in short-term memory. Here, we examined the feasibility of using resting state MEG oscillations to predict individual performance working memory. We recorded resting state MEG and administered the Working Memory Index (WMI) from the Wechsler Adult Intelligence Scale (WAIS-IV) and the Spatial Addition (SA) subtest from the Wechsler Memory Scale (WMS-IV) to assess WM performance in 18 participants (6 males and 12 females; mean= 26.5 years, SD= 3.98 years). We calculated means 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; gamma3 90-120Hz). MEG power normalized by the maximum in

each frequency band was correlated with WM performance at the sensor level. We applied non-parametric cluster mass analyses ($p<0.001$) to determine significant correlations between PSD at each frequency band and neuropsychological tests. We found correlations between MEG power and neuropsychological scores for WMI, SA that show clusters in the bilateral posterior and right fronto-temporal regions for the delta band, in the fronto-middle line and right temporal regions for the theta band, as well as in the parietal regions for the alpha band.WMI and SA shared a common correlation pattern with a fronto-parietal cluster of sensors but we also found clusters that were specific to each modality.

3-F-128 Genetic predictors of neurocognitive outcome in children treated for medulloblastoma

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Treatment for pediatric brain tumors impacts significant neurotoxicity on the developing brain. As a result, pediatric brain tumor survivors are at risk for significant long-term neuropsychological impairment. While current research has elucidated the negative effects of treatment on brain structure and cognitive ability in these patients, there remains variability in outcomes, and it is important to predict prior to therapy, those patients who will do better or worse. Single nucleotide polymorphisms (SNP's), genetic variations in the human genome that represent a single nucleotide base change in a strip of DNA, have been shown to predict neuro-toxicity in response to cancer treatment. In particular, glutathione-S-transferases and peroxisomal proliferator-activated receptors have been shown to be involved in DNA repair and modulation in response to brain damage. SNP frequencies of these two genes were related to the neuropsychological outcome of pediatric brain tumor survivors. Direct relationships were found between SNP frequencies at these genetic loci and outcome measures such that better-performing patients show similar allelic frequencies to healthy controls, and poor-performing patients show distinct allelic frequencies from healthy controls. Our data suggest that germ-line DNA may be predictive of intellectual outcome following treatment for medulloblastoma.

3-F-129 Role of the ventral hippocampal projections to the lateral septum in fear and anxiety

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In the present study, we investigated the behavioural contribution of the ventral hippocampus (vHPC)-lateral septum (LS) pathway in modulating anxiety-related behaviours in mice. We targeted the LS-projecting vHPC neurons by injecting the retrogradely propagating CAV-Cre into the LS and injecting Cre-responsive AAV (AAV-hSyn-DIO-hM3D (for activation) or hM4D (for inhibition) into the vHPC. After CNO injection, the animals were submitted to behavioural test paradigms for anxiety: elevated plus maze (EPM), and open field (OF), novelty feeding suppression test (NFST) and fear conditioning (FC). The activation of LS-projecting vHPC neurons using hM3d induced an increase in the open arm time in the EPM without changing the locomotor activity. Similarly, in the NFST the latency to eat decreased in the hM3D group compared with the control group. No alterations were observed in the OF in both locomotor and center time. In contrast, during the EPM exposure, the hM4D group showed an increased avoidance to the open arms compared to the control group. In the OF,hM4D group displayed a significant decrease in center time. During the FC, the activation of the LS-projecting vHPC neurons during the fear acquisition reduced freezing levels 24h after the acquisition in the hM3D group.

However, the inhibition of the same neuron population did not alter the freezing levels in the hM4d group. In summary, our findings demonstrate that the LS-projecting vHPC neurons modulate anxiety-related behaviours in a bidirectional manner, and their activation can reduce contextual fear memory expression.

3-F-130 The lateral entorhinal cortex encodes combinations of physical and relational features of stimuli in environmental context

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The entorhinal cortex (EC) is a critical part of the hippocampal memory system. Accumulating evidence suggests a functional division between medial and lateral subdivisions of the EC: whereas the medial region is particularly involved in spatial memory and navigation, the lateral entorhinal cortex (LEC) is necessary for context specific memory associations. To study how single neurons in the LEC encode information consisting of context-specific associations, we recorded single neuron activity in the LEC while rats received a neutral, conditioned stimulus (CS) alone or paired, 500 ms later, with eyelid stimulation (an unconditioned stimulus, US). Presentations involved two distinct CSs and two distinct conditioning chambers to examine coding for physical stimulus feature and environmental context. We found that many LEC neurons were sensitive to the physical stimulus feature, the associative relationship between CS and US, or environmental context, and that the majority of them showed the selectivity for more than one information type. At the population level, the selectivity of ensemble code was higher for the physical stimulus feature and environmental context than associative relationship. We also found that neuron ensembles in anterior-dorsal part of the LEC were more selective for all information types compared with those in the posterior-ventral part. These findings suggest that the LEC carries integrated information about stimuli, their environment, and relationship with reinforcer.

3-F-131 Basal forebrain cholinergic lesions attenuate the reinstatement of cocaine-seeking produced by a discriminative stimulus in goal-trackers but not sign-trackers

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Goal-trackers (GTs), compared to sign-trackers (STs), express higher levels of acetylcholine when performing a cue detection and processing task. We hypothesized that GTs utilize their basal forebrain (BF) cholinergic systems differently than STs. We investigated individual variation in the reinstatement of drug-seeking behavior produced by a signal indicating cocaine availability (discriminative stimulus) and the influence of the BF cholinergic system. STs and GTs were trained to self-administer cocaine using an Intermittent Access procedure which allowed animals access to cocaine for discrete 5-min drug available periods indicated by a light signal (DS) separated by 25-min no drug available periods indicated by a different signal (DS-). Next, animals underwent extinction training where the context was devoid of both DSs and an active response had no consequence. After behavior was extinguished, half of the subjects received bilateral infusions of the cholinotoxic immunotoxin 192 IgG-saporin into the BF, while the others received sham surgeries. Finally, animals underwent a reinstatement test during which the DS was presented non-contingently for 2 sec on a variable time schedule. ST-lesion group and both sham groups reinstated responding upon DS exposure. In contrast, the GT-lesion group did not reinstate responding and had fewer active responses than the GT-sham group. Our findings suggest that the BF

cholinergic system is involved in reinstatement of drug-seeking behavior produced by a signal indicating drug availability in some animals (GTs), but not others (STs).

3-F-132 Optical Imaging of Forgetting in the Mouse Hippocampus

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Throughout adulthood, new neurons integrate into the dentate gyrus (DG). Computational models predict that ongoing adult hippocampal neurogenesis (AHN) degrades previously-encoded memories by reorganizing DG-CA3-CA1 circuits, and consistent with this prediction, our lab found that increasing AHN post-encoding leads to forgetting. However, it remains unclear how forgetting is represented at the level of cell ensembles in the hippocampus. Since recapitulation of neuronal activity patterns present during encoding is thought to underlie successful memory retrieval, here we asked whether memory-related neuronal activity would be perturbed by neurogenic conditions that produce forgetting. Using miniaturized head-mounted microscopes and the genetically-encoded Ca2+ indicator GCaMP6f, we recorded activity from hundreds of CA1 neurons in freely moving mice during a contextual fear conditioning task (training, 1-day and 29-day test). One group of mice exercised for 28 days between tests to promote AHN (DCX+ cells) while the other group was housed conventionally. Ca2+ transients were extracted from individual CA1 neurons and analyzed for population activity measures. We found that running-induced increases in AHN induced forgetting of the context memory and altered CA1 population activity measures (e.g., changes in overall firing rates and proportion of activated neurons) relative to controls. These preliminary results reveal the functional consequence of AHN on population activity in the HPC and begin to address the neural circuit mechanism by which forgetting occurs in the brain.

3-F-133 Linking of fear memories by temporally limited changes in both excitatory and inhibitory neuron activity in the lateral amygdala

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Increased excitability associated with fear memory formation allows allocation of a second memory to an overlapping population of neurons in the lateral amygdala (LA). To investigate mechanisms by which co-allocation may occur we co-expressed channelrhodopsin2 (ChR2) and red-shifted halorhodopsin (NpHR) in a subset of neurons in the LA of mice, enabling neuronal excitation or inhibition in the same neurons by blue light and red light, respectively. Activation of ChR2 prior to auditory fear conditioning resulted in allocation of the fear memory to opsin-expressing neurons as indicated by inhibition of memory expression by NpHR activation. When mice were given a second distinct fear memory training session without ChR2 stimulation, the second memory could also be inhibited by NpHR if the two sessions occurred within the time frame of increased excitability (<6h), indicating that memories were co-allocated. When training sessions occurred outside the window of increased excitability (>24h), the second memory was insensitive to NpHR and thus allocated to a separate group of neurons. Memory co-allocation was also dependent on increased inhibition in the LA as the second memory was only dis-allocated by coincident inhibition of opsin-expressing excitatory neurons and local parvalbumin-positive interneurons. Collectively, these results show that memory formation results in increases in both

principal neuron and inhibitory interneuron activity,transiently constraining the population of neurons that are involved in subsequent memory formation, thereby promoting memory co-allocation.

3-F-134 Pathway-specific recording of thalamic input to nucleus accumbens during reward seeking task

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The nucleus accumbens (NAc) is a forebrain structure that is critically involved in decision making processes. Spiking activity in the NAc increases during the presentation of reward-associated stimuli, particularly when the stimuli provoke a behavioural response. Excitatory inputs to the NAc come from several brain regions. These inputs are generally thought to encode some aspect of external stimuli and internal states, but it is presently unclear what specific information is encoded in each discrete glutamatergic input. Here, using fiber photometry, we recorded activity specifically from thalamic inputs to the NAc in vivo to assess when this pathway is active in relation to reward seeking behaviour. Viral-mediated gene delivery was used to target expression of the calcium indicator protein GCAMP6s to intralaminar thalamic nuclei. A fiber optic was then implanted within the NAc to monitor GCaMP fluorescence from thalamic axons located there. Animals were trained to distinguish between two distinct tones, and an active lever press during one tone resulted in food delivery. We found that thalamic input to the NAc is not responsive to either reward-associated or neutral tones. However, increases in activity were observed when animals made rewarded lever presses. Additionally, there were dramatic decreases in thalamic activity during consummatory behaviour, and a subsequent rebound in activity upon exits from the food port. Overall, thalamic input to the NAc seems to encode aspects of volitional motor behaviour and is not especially responsive to external stimuli.

3-F-135 Neurocognitive alterations in adult rats following neonatal treatment with domoic acid

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Schizophrenia is characterized by cognitive abnormalities which can be modeled in rodents. The study assessed cognitive flexibility, short-term memory (STM), long-term memory (LTM), and problem solving ability using the attentional set-shifting paradigm (ASSP) and puzzle box paradigm (PBP) in an animal model of schizophrenia. Sprague-Dawley rats (n=40) were given subcutaneous injections of either saline or 20 mcg/kg of domoic acid (DOM) from postnatal day 8-14 and tested in adulthood in each paradigm. The ASSP assessed ability to solve discrimination problems in order to obtain a food reward by attending to a relevant cue while ignoring an irrelevant cue. Cues are shifted and cognitive flexibility measured by trials to criterion (six consecutive correct choices). The PBP measured latency to pass from an aversive box separated by a barrier into a rewarding box. Novel barriers were present in "problem solving tasks"' recently faced barriers in "STM tasks"' and remotely faced barriers in "LTM tasks". It was hypothesized that DOM-treated subjects would show cognitive deficits in each paradigm. Results showed improved cognitive flexibility in the ASSP and improved STM and problem solving ability in the PBP in DOM-treated subjects. Findings were in contrast to the hypothesis and may be related to increased response to novelty, thereby promoting enhanced attention to challenges, which has been reported in the clinical population. Future directions include more formal assessments of response to novelty in order fully characterize the response pattern observed in the current study.

3-F-136 Metformin promotes cognitive recovery in two mouse models of juvenile brain injury

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Endogenous repair strategies used to activate neural precursor cells (NPCs) and promote functional recovery after brain injury have shown tremendous promise. We sought to determine the potential of metformin (met) to promote behavioural recovery in mouse models of juvenile brain injury. Previous work demonstrated one week of met treatment was sufficient to promote functional motor recovery and enhanced neuro- and oligogenesis following hypoxia-ischemia (H-I) in neonatal mice. We hypothesized that met treatment would also promote cognitive recovery and performed our analysis in two different injury models. First, mice received the H-I insult at postnatal day (PND) 8 and received 5 weeks of met treatment. Strikingly, H-I injured mice displayed long term deficits in executive function that were completely recovered following met treatment. In a second model, PND17 mice received cranial irradiation (IR) to mimic the cellular and cognitive deficits observed in children who received IR as treatment for medulloblastoma. Mice were subjected to multiple cognitive assessments and most interesting, we observed gender specific impairments in IR mice. Moreover, when mice were administered met for 25 days, cognitive deficits in females were rescued but there was no improvement in males. We are beginning to address the cellular basis for these observations using the neural stem cell colony forming assay as well as tissue analysis. To date, our data reveals that met treatment is effective at promoting cognitive recovery in two juvenile brain injury models.

3-F-137 Insights into how the Hippocampus Governs the Drive to Explore

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Exploration is a fundamental and phylogenetically conserved behaviour that is crucial for efficient learning and favourable adaptation in changing environments. In addition, perturbed exploratory behaviour is often found in mental illness, and better understanding the mechanisms that give rise to exploratory drive could contribute to superior treatment strategies for psychiatric disease. In humans and mice, hippocampal function is tightly linked to the drive to explore novelty in non-stressful environments. Here we present data on the roles of cortical and subcortical innervations to the hippocampus in specific forms of exploratory drive, as well as global molecular changes in the hippocampus that correlate with exposure to a novel environment. Our methods included optogenetics, microdialysis and electrophysiology in freely-behaving mice, mass spectrometry mediated proteomics, positron emission topography and ofMRI. These preliminary results help elucidate novel circuits and molecules underlying the drive to explore in health and disease.

3-F-138 Involvement of CB1 receptor on fear memory processing and on long-term potentiation in the hippocampus and infralimbic cortex.

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Recent evidence confirm the involvement of the hippocampal CB1 receptors in the modulation of both memory extinction and reconsolidation processes in different brain areas, but few studies focused on the infralimbic cortex, another important cognitive area. Here, we infused the cannabinoid agonist CP55,940 either into the infralimbic cortex (IL) or the CA1 area of the dorsal hippocampus (HPC) of adult male Wistar rats immediately after a short (3min) reactivation session, known to labilize a previously consolidated memory trace in order to allow its reconsolidation with some modification. In both structures, the treatment was able to disrupt reconsolidation in a relatively long lasting way, reducing the freezing response. To our notice, this is the first demonstration of endocannabinoid system involvement in reconsolidation in the Infralimbic Cortex. CP55,940 is a potent agent, and these results suggest that a similar CB1-dependent circuitry is at work both in HPC and in the IL during memory processing. In electrophysiology, a concentration of CP55,940 compatible with that found effective upon fear memory, block LTP induction vivo. However, these results reinforce and diversify previous findings, including some from our own lab, that prove the involvement of CB1 receptors in memory consolidation, retrieval, reconsolidation and extinction as well as possible plastic changes in receptor density due to the cognitive experience, tha is necessarily mediated by plastic synaptic events such as LTP.

3-F-139 N400 evidence for embodied processing of concrete words after a picture context

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Previous neurolinguistic research has revealed that word recognition is sensitive to prior contextual information that is present in the wider linguistic discourse. The current research used ERPs to investigate whether context effects on word recognition are also influenced by contextual cues that are provided by non-linguistic information. In the experiment 25 participants (20 female) listened to sentences, such as He could not hide his anger/delight upon hearing the news, designed such that the alternative critical words were equally acceptable within the local sentence context. Sentences followed a context-providing image rendering one of the critical words semantically anomalous (e.g., an image of a man with a happy expression). Relative to the context-congruent alternative, context-anomalous words elicited an N400 effect that started at 300-330 ms post acoustic word onset. This effect had a typical centroparietal distribution, with a right hemisphere bias. Furthermore, generalized additive mixed models revealed that this N400 effect was modulated by the concreteness of the critical word. In congruent contexts, highly concrete critical words elicited smaller N400 waveforms compared to abstract critical words. However, the same effect of concreteness was not observed in context-anomalous trials. The overall results support the claim that context can yield a strong expectation for a particular upcoming word. We also demonstrate the novel finding that a contextual constraint effect on word recognition interacts with lexical characteristics such as concreteness.

3-F-140 The neural basis of episodic memory transformation in humans

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As memories for events age and lose detail, how do the brain networks supporting these memories change? We used fMRI to test the neural correlates of episodic memory transformation in the human brain. During fMRI scanning, participants viewed a series of film clips of episodes. Immediately after, they were cued to retrieve the memory for half of the film clips they had just seen. Seven days later,

participants returned to the scanner and were cued to retrieve the other half of the film clips. During the immediate memory test, participants report richly detailed episodic memories for the film clips, and have high hippocampal activation during memory retrieval. Seven days later, participants show a reduction in memory for the details of the film clips, but retention of memory for the general storyline, supported by a reduction of hippocampal activation, and an emergence of activity in the prefrontal cortex, a brain region found to be activated during remote episodic memory retrieval in humans. Critically, when the memories retained their vividness, hippocampal activity was comparable during immediate retrieval and 7d retrieval sessions, suggesting that the hippocampus continues to be important for the retrieval of detailed episodic memory.

3-F-141 An anatomical interface for guidance of visual behavior by medial temporal lobe representations

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Visual behavior is guided by memories from previous experience and knowledge of the visual scene. Amnesic cases, those with damage to the medial temporal lobe (MTL) and specifically the hippocampus, do not exhibit effects of memory in their visual behavior. This suggests that MTL memory representations can bias the selection of saccades. However, no direct connections are known to exist between MTL and oculomotor control areas, and how memory representations from the MTL influence the oculomotor system remains unknown. Using network analysis, we examined the neuroanatomical basis for the routing of memory information to oculomotor structures. We derived a connectivity matrix from a database of macaque axonal tract tracing studies that included 75 cortical and subcortical ROIs from the visual, oculomotor and memory systems. Using a data-driven iterative force-directed layout procedure, we detected two distinct processing streams that each represented the visuo-oculomotor and memory systems. We identified a putative set of hub regions that densely interconnect the oculomotor and memory streams. These included the ventro- and dorso-lateral prefrontal cortices, the posterior cingulate, the inferior parietal lobule, the parahippocampal cortex and the supplementary eye field. Interestingly, the frontal eye field also emerged as a hub, suggesting that it is well positioned to directly integrate memory information into the guidance and control of saccades. Our findings reveal a network of areas that together may mediate the moment-to-moment influence of memory on visual behavior.

3-F-142 GABA Cells in the Central Nucleus of the Amygdala Control Cataplexy

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Cataplexy is a debilitating symptom of narcolepsy characterized by the sudden loss of muscle tone during wakefulness. The neural mechanism underlying cataplexy is not well understood, but since it is often triggered by strong positive emotions, the amygdala is hypothesized to control cataplexy onset. We used chemogenetic, electrophysiological, and behavioural techniques to identify a GABA circuit in the central nucleus of the amygdala (CeA) that may play a causal role in promoting cataplexy. The CeA of 13 orexin-/-,VGAT-Cre mice was bilaterally injected with 200 nL of an AAV containing an excitatory DREADD expressed in GABA cells (AAV/hSyn-DIO-hM3Dq-mCherry). Neurons expressing this receptor are activated by clozapine-N-oxide (CNO). EEG, EMG, and video data were collected overnight following CNO or saline (control) injections. We found CNO-induced activation of GABA CeA cells increased time

mice spent in cataplexy ($p<0.001$), triggering more episodes ($p<0.01$) without changing their duration. Levels of muscle atonia, theta activity, and episode duration were identical under both saline and CNO conditions. We also found the CNO-induced cataplexy was mainly associated with positive stimuli such as wheel running ($p<0.01$), and the increased attack frequency arose from a reduction in the threshold to elicit cataplexy ($p<0.05$). Our data suggest that emotionally rewarding stimuli may trigger cataplexy by activating GABA CeA cells. Understanding downstream regions through which the CeA produces cataplexy is an important next step in dissecting cataplexy mechanisms.

3-F-143 Memory functions of adult neurogenesis are modulated by stress and sex

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The discovery that new neurons are born in the adult brain has opened the door to exciting possibilities by which experience can sculpt circuits and modify behavior. Rodent studies have shown that immature neurons are more plastic than pre-existing neurons and while there is evidence that they make functional contributions to memory their exact role remains unclear. There is a growing body of work indicating that newborn neurons regulate emotional behaviors in response to stress. To test a stress-dependent function for new neurons in memory we trained neurogenesis-deficient GFAP-TK rats in the spatial water maze under high (16°C) or low (25°C) stress conditions. We find that, in male rats, blocking adult neurogenesis indeed impairs spatial learning and memory primarily at cold, stressful temperatures. Since males and females differ in stress reactivity, and little is known about functions for new neurons in males vs. females, we then examined how stress modulates learning and memory in female rats that lack neurogenesis. In contrast to males, neurogenesis-deficient female rats were not impaired when trained at 16°C, and even showed a trend for enhanced performance relative to their wild-type littermates. Furthermore, whereas temperature did not affect wild-type female rats, neurogenesis-deficient female rats performed significantly better and had greater corticosterone levels at 16°C than at 25°C. Collectively, our data indicate that adult neurogenesis regulates learning under stress and additionally suggests that new neurons perform distinct functions in males and females.

3-F-144 Hippocampus place cell network properties in a Fmr1 knockout model of Fragile X Syndromic Autism Spectrum Disorder

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The hippocampus (HPC) is a neural system that is crucial for high-order cognitive functions such as autobiographic memory, spatial navigation, and cognitive control. The HPC place cell (PC) network is hypothesized to form the cognitive map that enables these functions. Deficits of cognitive control--inability to use relevant information while ignoring distraction--are a core feature of Autism Spectrum Disorder (ASD). We characterized properties of PCs in a Fmr1-knock out (KO) mutant mouse model of Fragile X Syndrome, that has a high prevalence of Autistic features. HPC PCs were recorded concurrently with local field potentials in CA1 while wild-type (WT) and Fmr1-KO mice first explored an open-field, then performed active place avoidance tasks designed to evaluate cognitive control. During open-field exploration, Fmr1-KO PCs formed normal place fields and did not differ from WT discharge properties. Analysis of the Fmr1-KO PC network revealed hyper-stability estimated by the spike-field phase-frequency relationship. The Fmr1-KO mice learned place avoidance equivalent to WT, demonstrating ability to acquire and use task information. During an second extinction session that followed an initial

extinction and reinstatement session, Fmr1-KO avoidance behaviour persisted compared to WT even though task demands changed, suggesting cognitive inflexibility. Largely intact but hyperstable place cell discharge properties under constant conditions suggest that cognitive inflexibility can arise from hyperstability in cognitive representations in HPC and perhaps other brain regions.

3-F-145 Programming of adult behaviour and epigenetic gene regulation in rat offspring through prenatal exposure to predator odour

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Stress mediated through the mother can lead to long-term alterations in stress-related phenotypes in offspring. Predator odour is an ethologically relevant psychological stressor in rodent species. We previously reported that prenatal stress by predator odour enhances predator-odour induced defensive, endocrine, stress and epigenetic response to predator odour exposure in adult mice. The present study was designed to examine the effects of prenatal predator odour exposure in adult rats. Further, we examined performance on anxiety-like behaviour using standardized tasks that assess approach-avoidance conflicts. Pregnant rats were exposed daily to predator odours or water control over the second half of pregnancy. As adults, the offspring of predator odour-exposed mothers showed increased anxiety-like behaviors in standardized tasks and sex-specific anti-predatory behaviour and endocrine stress reactivity in response to predator odour exposure. A specific increase of FKBP5 transcript abundance in the amygdala of adult female offspring of predator odour-exposed mothers correlated with a site-specific decrease in amygdala DNA methylation of FKBP5 intron V, suggesting a contribution of this epigenetic mechanism to programming by prenatal predator odour exposure. Maternal predator odour exposure alone is sufficient to induce an altered stress-related phenotype in adulthood, both toward standardized and naturalistic stressors in offspring. In adult females, these effects are accompanied by long-term changes in gene expression and epigenetic modifications in limbic regions.

3-F-146 Feedback inhibition underlies slot-like capacity and resource-like neural coding: a biophysical model of multiple-item working memory

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For the past decade, research on the storage limitations of visual working memory (WM) has been dominated by two fundamentally different hypotheses. One posits that memoranda are stored in a small number of "slots". The other posits that a limited "resource" can be allocated to any number of items N, but with increasingly poor resolution. These hypotheses have characterized the computational structure of WM, but neither provides a complete account of the available data, and neither speaks to the neural basis of storage limitations. To address these shortcomings, we used a biophysically-based cortical model to simulate multiple-item WM tasks. The model's cellular resolution allowed us to quantify the coding fidelity of memoranda with established statistical measures for single-neuron activity. Our simulations reproduce a wealth of neural and behavioural data from human and non-human primate (NHP) studies of WM, and demonstrate that feedback inhibition not only lowers capacity by inducing competition, but also lowers coding fidelity. Because the strength of feedback inhibition tracks the number of item-encoding neural populations, increasing N progressively lowers fidelity until capacity is reached. As such, the model provides a mechanistic explanation for experimental data showing a reduction in WM precision with increasing N, where precision plateaus at

capacity. Crucially, the model makes specific predictions for single-neuron data from multiple-item tasks with NHPs, allowing our unifying hypothesis to be tested by established electrophysiological and behavioural methods.

3-F-147 Remote object memory destabilization involves a pathway linking M1 receptors to proteasome-mediated protein degradation

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Consolidated memories can become destabilized during retrieval, presumably for updating or maintenance. Destabilization of remote memories is most reliably prompted by the presence of novelty during reactivation. Moreover, activation of muscarinic cholinergic receptors (mAChRs) at the time of reactivation facilitates destabilization of older engrams, in keeping with the role of acetylcholine in attention and new learning. Likewise, targeted protein degradation via the ubiquitin proteasome system (UPS) is required for destabilization of fear and object location memories. Given the established role of calcium in regulating proteasome activity, we hypothesized that intracellular calcium mobilized by M1-type mAChR activation of inositol triphosphate (IP3) plays a role in activating the UPS. Accordingly, we investigated the roles of mAChR subtypes, IP3, and proteasome activity in remote object memory destabilization using microinfusions into the perirhinal cortex, a brain region strongly implicated in object memory. Findings revealed dissociation between mAChR subtypes: an M1, but not an M2, mAChR antagonist blocked destabilization in the presence of novelty. Likewise, the novel M1 agonist CDD-0102A (1 μg/μl) facilitated destabilization in the absence of novelty. Both the IP3 inhibitor xestospongin (0.2 ng/μl) and the proteasome inhibitor β-lactone (32 ng/μl) equally blocked destabilization. Lastly, an interaction was found between M1-type mAChRs and both IP3 and proteasome activity. This research has the potential to expand our understanding of memory modification.

3-F-148 Do multivoxel patterns of activity within the hippocampus carry information about temporal duration contained within event sequences?

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The hippocampus (HC) is believed to play an important role in processing temporal information in the service of episodic memory. Evidence for this in humans comes from studies that have examined the temporal context and order in which events occur. However, it is unclear if the HC also plays a role in the processing of temporal duration, for instance, memory for elapsed time between successive events. Suggestive of this, we recently demonstrated HC activity is sensitive to the durations of intervals separating events within a sequence (Barnett et al., 2014). Notably, this finding was in the context of a task in which participants explicitly monitored duration, which differs from the implicit processing of duration typically associated with everyday episodic memory. Here, we used fMRI to scan healthy participants during a match-mismatch detection task in which subjects monitored the order of event sequences. Crucially, unknown to the participants, the interval durations within each sequence were manipulated between encoding and test, allowing us to examine neural activity associated with implicit memory for temporal duration. Analysis of multivoxel activity during encoding and retrieval of sequences revealed differential patterns associated with the representation of order and duration memory in the HC, prefrontal cortex and regions typically associated with timing. Our results offer

further insight into the role of the HC in temporal memory, providing evidence that episodic memory for sequences contains information about temporal duration structure.

3-F-150 Neurogenesis' Influence on Learning and Memory: A Computational Approach to Dynamics of Circuit Remodeling

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The continuous addition of new neurons to adult hippocampal circuits has been shown to induce forgetting of previously learned memories corroborating the findings of computational models that predicted these effects. However, the precise mechanisms mediating these neurogenesis-dependent forgetting effects are unclear. Here we developed a three layer feed-forward neural network to represent the hippocampus, with the input, middle, and output layers representing the entorhinal cortex, dentate gyrus and CA3 regions, respectively. We trained the network on a set of patterns and then, to model ongoing hippocampal neurogenesis, we added new neurons to the middle layer. Consistent with our in vivo results, addition of new neurons reduced retrieval success for learned patterns. Forgetting in this instance could be related to the addition of new neurons, new connections or both. In order to discriminate between these possibilities we manipulated neuron number, as well as input and output connectivity to the middle layer. The results from this model will provide a mechanistic framework for understanding neurogenesis-mediated forgetting in the hippocampus.

3-F-151 Excitability of human dorsal premotor cortex and ipsilateral primary motor cortex interactions prior to grasp

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Dorsal premotor cortex (PMd) is involved in the selection, preparation and execution of voluntary action. Monkey neurophysiology and human neuroimaging indicate that PMd encodes grasp. Paired-pulse transcranial magnetic stimulation (TMS) with two coils was used to test functional interactions between left PMd and ipsilateral primary motor cortex (M1) while at rest or during preparation to grasp objects with either a precision grip or a whole-hand grasp. The test stimulus (TS) was applied to M1 with a small branding coil (50 mm diameter). The TS intensity was adjusted to evoke a motor evoked potential (MEP) amplitude of ~1mV. Another branding coil (40 mm diameter) was used to deliver the conditioning stimulus (CS) to PMd. The CS was set at 90% of the active motor threshold (AMT). Interstimulus intervals (ISI) of 4, 6, and 8 ms between CS and TS were used. We show that when planning to grasp objects with either a precision grip or a whole-hand grasp, PMd facilitates excitability levels in M1 hand representations. We also found that MEPs in the hand muscles during grasp preparation are associated with the pattern of muscle activity used in the upcoming grasp. We found that the degree of MEP facilitation was larger when conditioning PMd (PMd-M1 interactions) compared to conditioning M1 (paired-pulse M1). These findings provide causal evidence that human PMd transfers grasp-related information to M1 hand representation during the preparation for an upcoming grasp.

3-F-152 Interrogation of a Fear Memory Network

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The recall of consolidated fear memories requires coordinated activation of a broad network of brain regions. Previous work from our lab has identified the inter-regional co-activation patterns across 84 different brain regions during memory recall, by mapping the expression of the activity-dependent early gene c-Fos. Graph theoretical analyses of this functional network revealed several highly-connected regions called hubs, which are likely to be central for the overall network integrity. We predicted that deletion of these hub regions will have the most severe impact on network function and consequently, memory performance. To test this theory, we used a propagation model to examine the impact of deletion of regions with high vs. low connectivity on network function in silico. Next, we performed in vivo experiments, where we silenced either hub and non-hub brain regions following fear conditioning, using a DREADDs approach (hM4Di). In silico, we found that deletion of hub regions had the greatest impact on network function (e.g. significant reductions in global efficiency). Importantly, the same effect was observed in vivo, where inhibition of hub regions specifically caused deficits in memory recall. In our current experiments we are exploring identified hubs in more detail. In particular, we have used optogenetic approaches to characterize the role of the anterodorsal thalamus in fear memory consolidation and retrieval. Together, our results demonstrate that functional connectivity is a reliable predictor for regions that are necessary for memory recall.

3-F-153 Dissociable contributions of dopamine D1 and D2 receptors to regulation of rule-guided oculomotor behaviour by dorsolateral prefrontal cortex

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Dopaminergic neuromodulation of the executive functions of dorsolateral prefrontal cortex (DLPFC), via the D1 and D2 receptor families (D1Rs and D2Rs), has been of considerable interest due to the psychiatric implications of dopaminergic dysfunction. Studies of oculomotor spatial working memory (WM) in DLPFC have shown that D1R stimulation dose-dependently augments and deteriorates mnemonic activity, while D2R selectively affects perisaccadic activity, putatively encoding motor feedback or corollary discharge. Recently, both D1R and D2R stimulation in DLPFC were shown to augment WM activity for abstract rules in a non-oculomotor paradigm. Here, we examined D1R and D2R microiontophoretic stimulation of DLPFC neurons engaged in an oculomotor pro/antisaccade task involving rule representation in WM to guide appropriate target selection. We found dissociable effects of D1R and D2R stimulation on DLPFC task-related physiology and behavioural performance. D1R stimulation degraded rule and saccade selectivity, augmented sensory coding while increasing impulsive responding and rule-selective performance errors. D2R stimulation had ambivalent effects on rule and sensory representation, but selectively augmented presaccadic selectivity preferentially for prosaccades, sparing task performance. Our results suggest that DLPFC D1Rs and D2Rs play dissociable roles in rule maintenance with D1Rs involved in both mnemonic performance and impulse control, while D2Rs play a selective role in modulating oculomotor dynamics unrelated to motor feedback, and not rule representation.

3-F-154 Generation of neural trajectories with oscillations in the absence of ongoing external stimulation

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It is an open problem how cortical circuits can produce specific patterns of activity in the absence of ongoing external stimulation (Laje and Buonomano, 2013). Many cognitive and behavioral tasks require continuous neural activation in the absence of external inputs. For instance with interval timing no other stimulation than a "GO" cue is available for the underlying neural substrate to generate the appropriate response. In this study, we propose a new model based on reservoir computing, where an output unit is taught to produce a complex time-varying series as it reads the activity of a recurrent networks (reservoir). We show that when we drive the reservoir with periodic inputs, regardless if it is in a stable of chaotic state, we can produce meaningful and repeatable neural patterns. The model uses a layer of oscillators with different periods where their phase are aligned in a specific configuration on every trial in order to produce the required input waveform. This model is well supported by the architecture of the olivo-cerebellar circuit, where the inferior olive project oscillatory activity in the cerebellum which is thought to be responsible for motor control and interval timing (Llinas, 2009). We show that on a timing task, this model is superior to the performance of the previous implementations on all aspects while being resistant to relatively large perturbations of its state or parameters. Our work propose a previously unknown role for neuronal oscillations, namely the production of repeatable and stable time-varying patterns in cortical circuits.

3-F-155 Levodopa impairs learning in healthy young adults: Implications for levocarb in Parkinson's disease

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Dopaminergic therapy improves some cognitive functions and worsens others in patients with Parkinson's disease. These paradoxical effects are explained by the dopamine overdose hypothesis, which proposes that effects of dopaminergic therapy on a cognitive function is determined by the baseline dopamine levels in brain regions mediating that function. We directly tested this prevalent hypothesis, evaluating the effects of levodopa on stimulus-reward and stimulus-response learning in healthy young adults. Half of participants were tested on 100/25 mg of levocarb whereas the other half were tested on an equal volume of placebo in a randomized, double-blind, placebo-controlled design. Participants treated with levodopa demonstrated significantly poorer learning performance than those treated with placebo. In two separate manners, we demonstrated that levodopa impairs learning of stimulus-reward and stimulus-response associations in healthy young adults with optimal endogenous dopamine levels and regulation. Our findings support the notion that brain regions replete of dopamine are sensitive to overdose by dopaminergic therapy. Critically, these effects are independent of Parkinson's disease pathology, severity, and receptor sensitization from chronic exposure to medication.

3-F-156 Behavioral effects of CCK-GABA neurons: implications for schizophrenia

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Disrupted ã-aminobutyric acid (GABA) signaling is a hallmark of several neurological disorders. Recently, it has been suggested that GABAergic neurons which express the neuropeptide cholecystokinin (CCK-GABA neurons) contribute to the pathogenesis of schizophrenia. Reduced CCK-GABA neuron activity, which is observed in animal models of schizophrenia, is associated with impaired network oscillations and behavior. Given that reduced CCK-GABA neuron activity may contribute to deficits in schizophrenia, it is possible that activating CCK-GABA neurons may be therapeutic and rescue function. To determine

the behavioral effects of activating CCK-GABA neurons, we used a chemogenetic model. Transgenic mice were generated which expressed the synthetic excitatory receptor, HM3Dq, selectively in CCK-GABA neurons (HM3Dq::CCK-GABA mice). Prior to behavioral testing, these mice were given an injection of either the synthetic HM3Dq receptor-specific agonist clozapine-N-oxide (CNO) or saline. The results showed that CNO-treated mice had slightly increased anxiety in the elevated plus maze but enhanced performance in the novel object recognition, puzzle box and fear conditioning tests relative to saline-treated controls. These surprising results indicate that activating CCK-GABA neurons can indeed have beneficial effects on behavior, though at the expense of increased anxiety. The HM3Dq::CCK-GABA mouse line presents as a useful model to study the behavioral functions of CCK-GABA neurons, as well as the mechanisms of behavioral impairments in schizophrenia.

3-F-157 Event-related Brain Potentials and Oscillatory Changes in Response to Semantic and Syntactic Aspects of Sentence Processing

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While semantic and syntactic aspects of sentence processing elicit well-known event-related brain potentials (ERPs), their corresponding oscillatory responses (i.e., changes in power due to event-related synchronization, ERS, or desynchronization, ERD) are less clear. ERS/ERD, which do not rely on averaging in the time-domain, are more sensitive than ERPs to neural responses that vary temporally across trials, and can provide new insights into the brain's processing of semantic and syntactic information. Twenty adults (11F, mean: 28yr) watched 5 short animated films in which they heard correct sentences or matched sentences containing meaning or syntactic violations while wearing 64-channel EEG caps. ERPs and ERS/ERDs were compared for critical words in correct versus violation sentences. ERP results were as expected: a N400 in response to semantic violations and a Left Anterior Negativity/P600 to syntactic violations. Also, for semantic violations, a significant beta ERD (14-24 Hz) at frontal electrodes between 250-400 ms, followed by low theta ERS (3-7 Hz) at medial central/posterior sites between 500-1000 ms was seen. For syntactic violations, participants exhibited significant ERS in theta (4-7 Hz) throughout the whole 1s interval, most prominent at medial central/posterior sites. Both beta ERD and theta ERS are thought to reflect increased engagement of task-relevant brain areas underpinning semantic and syntactic processing. Results will be discussed in terms of the brain networks underlying the processing of these violation types.

3-F-158 The Theory of Mind network: brain connectivity patterns underlying ToM processing in adults

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Theory of mind (ToM) is the ability to understand that others can have mental states, beliefs, and knowledge different from one's own. ToM is crucial for healthy social interactions and interpreting social cues. Although studies have investigated brain areas activated during ToM processing, the relation between activated regions and the timing of activations within this complex network are unknown. We used 151-channel whole-head CTF magnetoencephalography (MEG) to image 23 typical adults (12 F, ages 20-35 yrs) as they performed a ToM task involving understanding whether a character on screen had a true or false belief. MEG data were co-registered to a T1-weighted structural MRI (Seimens Trio 3T). Time series from 90 brain regions of the AAL atlas were estimated using the LCMV beamformer,

filtered at theta (4-7Hz), alpha (8-14Hz), and beta (15-30Hz) bands, and phase data extracted using the Hilbert transform. Connectivity between regions was estimated with the Phase Lag Index. Partial Least Squares statistics were used to identify connections that showed significant activity changes during ToM processing. We found significant increases in connectivity between the false and true belief conditions. In alpha, the right angular gyrus (rANG) acted as a hub connecting bilateral parietal and left temporal nodes with the right inferior frontal gyrus (rIFG). In beta, the rIFG connected left mid frontal nodes with the rANG. ToM processing in an adult control population recruits long-range synchrony in the brain driven by the rANG and rIFG in both alpha and beta frequency bands.

3-F-159 Parvalbumin-positive interneurons modulate hippocampal-cortical coupling and fear memory consolidation

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As a memory undergoes consolidation, it becomes less reliant on the hippocampus (HPC) and more dependent on the medial prefrontal cortex (mPFC) for retrieval. Rhythmic oscillations in the mPFC, including delta waves and spindles, coincide with oscillations in the HPC, called sharp-wave ripples, and this oscillatory coupling across brain regions is thought to facilitate memory consolidation. While parvalbumin-positive interneurons (PVNs) fire in synchrony with spindles and ripples, whether they contribute to mPFC-HPC coupling, and by doing so, modulate memory consolidation, is unclear. Here, we combine the designer receptor approach with behavior experiments and in vivo recording in freely-behaving mice, to manipulate PVNs, and investigate their roles in memory consolidation. PV::Cre mice were infused with Cre-recombinase-dependent virus carrying the designer receptor hM4Di, which allows PVNs to be silenced by the designer drug clozapine-N-oxide (CNO). After surgery, mice were trained using contextual fear conditioning, then we silenced the PVNs. When mPFC or HPC PVNs were selectively inhibited during the consolidation period following conditioning, mice showed memory deficits. Electrophysiologically, we found that fear learning enhanced the probability of coupling between ripples, and cortical delta waves and spindles. This enhancement was attenuated when mPFC or HPC PV+ cells were silenced. This suggests that PVNs help coordinate mPFC-HPC co-activation, and interfering with their activity disrupts mPFC-HPC communication, and impairs memory consolidation.

3-F-160 Effects of cognitive training on motor skills in elderly

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It is well known physical exercise can reduce falls risk and improve cognitive functions in older people. Recently, studies have evaluated cognitive and dual task interventions on balance and gait. The aim of this study was to determine the effects of cognitive training intervention on agility and strength of lower limbs and depressive symptoms in older people. Participants (n = 60, aged 70.65 %2B 5) were randomly allocated to a cognitive training group (TG; n=30) or to a control group (CG; n=30). The TG completed a 12 week program with 24 sessions of executive functions, memory and math training. The following measures were assessed before and after intervention: Timed Up and Go Test - agility, Sit - Up Chair Test - strength and Geriatric Depression Scale - depression symptoms. A linear mixed-model analysis of variance (ANOVA) was used to compare differences between and within groups. Statistical analyses were performed with SPSS 21 and significance level was 5%. TG increased agility and strength scores and depressive symptoms was significantly reduced in compared with CG ($p < 0,001$) and the effect size was

0,48; 0,40; 0,47 respectively. The results showed intervention effect on all dependent variables. The outcomes indicated that cognitive stimulation was effective to promote motor skills and depressive simptoms improvement in healthy elderly.

G – Novel Methods and Technology Development

3-G-161 Plasma ADAM10 level as a potential biomarker for traumatic brain injury

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Traumatic brain injury (TBI) is the leading cause of disability and mortality in Canadians <45 years old. The majority of TBI incidences display diffuse and heterogeneous signs and symptoms that may go undetected by conventional diagnostic methods. Determining TBI occurrence is important to provide timely care to reduce risk of re-injury and exacerbation. Thus, there is an ever increasing amount of research focused on blood-based "biomarkers" of injury allowing for more objective diagnoses. Such biomarkers include neural-derived proteins, which can cross the blood brain barrier. We have previously found that blood plasma levels of cellular prion protein (PrPC) is elevated following TBI in both animal and human samples. We surmised that increased expression of PrPC post-TBI and its concomitant turnover in the brain likely leads to this transient rise in blood levels. Consequently, we explored whether Adam10, an enzyme whose functions include constitutive shedding of extracellular PrPC, is also a novel biomarker for TBI. Using sensitive ELISA protein quantification and other biochemical methods, we determined that Adam10 is likewise elevated post-TBI in animals and human patients. Serial samples collected from patients over several days post-TBI shows Adam10 levels correlating with the patients' neurological status (Glasgow Coma Scale). More importantly, the changing levels of plasma Adam10 correspond to similar trends in PrPC levels assayed alongside. Together our findings show Adam10 as a novel biomarker for TBI, and in tandem with PrPC can improve diagnostic accuracy.

3-G-162 Closed-loop interruption of hippocampal ripples in macaque

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Hippocampal sharp-wave ripples (SWRs) are considered crucial for memory consolidation. Stimulation of the CA3 axon collaterals in the hippocampal commissure in rats interrupts sharp-wave ripples and leads to memory impairment. In primates, however, these commissural collaterals are limited. In this study, we strive to investigate whether or not ongoing hippocampal activity could be altered by stimulation of fornix fibers with the rapid response necessary to interrupt ripples. Stimulating electrodes were implanted bilaterally alongside the fornix in the macaque, together with microelectrodes targeting the hippocampus for recording SWRs. We implemented closed-loop ripple detection that triggered fornix stimulation, and recorded the effects on hippocampal activity. This system successfully interrupted hippocampal ripples, and suppressed the ripple-associated multiunit response. These results demonstrate possibility of interrupting primate hippocampal ripples using fornix stimulation. Due to largely conserved connections in humans, this approach may be a means for modifying other hippocampal events affecting humans, such as mesial temporal lobe seizures. Electrical brain stimulation, e.g. vagus nerve and thalamic stimulation, has been used for treatment of seizure; post-stimulation suppression of multiunit activity, shown in our results, nominates fornix as a potential target for closed-loop stimulation and interruption of epileptic activity, as well.

3-G-163 Microfluidic manufacture of RNA-lipid nanoparticles leads to highly efficient delivery of potent nucleic acid therapeutics for controlling gene expression

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Lipid nanoparticles (LNPs) are used to deliver nucleic acids in vitro and in vivo. Here, we describe the robust manufacture and use of clinical-grade lipid-based nanoparticles for nucleic acids delivery at scales suitable for both in vitro screening and in vivo applications. We have conducted studies to evaluate the merits of the technology and further provide insights for delivering short interfering RNA (siRNA) and mRNA. RNA-LNPs were formulated to encapsulate a potent siRNA directed against PTEN. Exceptional cellular uptake (>98%) with minimal toxicity was observed in both primary rat hippocampal and mixed cortical cell cultures. High transfection efficency (>95%) of the encapsulated material resulted in high-level (>85%) PTEN knockdown within the first 4 hours of a low dose (100 ng/ml) treatment; knockdown was sustained for 21 days. Similarly, RNA-LNPs encapsulating mRNA were also found to mediate early (< 4 hours) and sustained gene expression (>75% for 7 days) following a single (500 ng/ml) treatment in primary rat mixed cortical cultures. Strategies for locally administering RNA-LNPs into the brain and spinal cord of adult Sprague Dawley rats were also investigated. Localized injections of PTEN-encaspulated siRNA into the motorcortex resulted in significant and sustained (7 days) knockdown. Similarly, local administration at the site of a cervical spinal cord injury significantly reduced target PTEN expression, 10 days later. Collectively, these studies reflect the simplicity and efficacy of this technology in validating new targeted nucleic acid therapies.

3-G-164 Development of a two-photon optogenetic tool box 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 present in various cell types. In neurons, cAMP and cGMP signaling pathways are crucial for synaptic plasticity and also learning and memory, however, their precise spatiotemporal roles and signaling interactions at synapses are not fully known. To study spatiotemporal cAMP and cGMP function in synaptic plasticity, we report two-photon optogenetic tools for controlling their signaling activity at the synapse by various wavelengths of two-photon excitation light. To dissect the role of postsynaptic cAMP in synapse structural plasticity, we previously utilized two-photon laser light excitation with a photoactivatable adenylate cyclase (PAC) and its mutant (BlgC), which synthesize cAMP and cGMP, respectively, in response to blue light. To expand the technique using other wavelengths of excitation light, we examined various photoactivatable enzymes sensitive to blue, green and far-red light. These photoactivatable enzymatic proteins were rapidly photoactivated and inactivated upon removal of light. We tested the activity of each enzyme across the two-photon excitation spectra in vitro. Longer wavelengths of two-photon light (>1,000 nm) efficiently photoactivated 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 the possibility of combining these two-photon optogenetic tools to manipulate cAMP and cGMP levels independently at synapses in living neurons.

3-G-165 MRI-guided focused ultrasound delivery of AAV6 and AAV1/2 to the brain under control of the neuron-specific synapsin promoter

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Background: The presence of the blood brain barrier (BBB) impedes delivery of most therapeutics from the blood to the brain, including adeno-associated virus (AAV) serotypes 6 and the mosaic 1/2. As an alternative to intracranial delivery, MRI-guided focused ultrasound (MRIgFUS) treatment may be used to locally and transiently permeabilize the BBB, thereby allowing for targeted delivery of AAV to the brain after systemic injection. In order to limit transgene expression in non-target organs, the neuron-specific synapsin promoter was used. AAV6 and AAV1/2-synapsin transgene expression in the brain was compared and quantified using unbiased stereology. Transduction of non-target organs including the liver, heart, and muscle was quantified using droplet digital PCR (ddPCR). Hypothesis: Transgene expression under control of the synapsin promoter will suppress delivery to non-target organs, such as the liver, while AAV serotype will influence rates of transduction as measured by ddPCR. Results: AAV6-synapsin expressing green fluorescent protein (GFP) resulted in a significantly higher percentage of transgene-positive neurons in brain (including the cortex, hippocampus, and striatum) than AAV1/2-synapsin. The AAV6 serotype also showed lower levels of liver transduction as compared to the AAV1/2 mosaic serotype. Conclusion: AAV6-synapsin-GFP is a better serotype candidate than AAV1/2-synapsin-GFP for MRIgFUS-mediated gene delivery to the brain. AAV6-synapsin demonstrated higher expression efficiency in the brain, and lower transduction of the liver.

3-G-166 Construction of a head-mount fluorescent miniature microscope

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How information is encoded and stored in the brain is a long-standing fundamental question in neuroscience. We have previously shown auditory fear memory is more likely to be encoded by lateral amygdala (LA) neurons with elevated level of transcription factor CREB (Han et al., 2007, Han et al., 2009). However how the activity of these neurons with high level of CREB contribute to memory allocation during memory formation is not fully known. We hypothesize that neurons overexpressing CREB have a higher baseline firing rate, and have increased response to tone during and after conditioning. In order to record and distinguish neurons overexpressing CREB and their neighbours in freely moving mice and test this hypothesis, we designed a miniature microscope that is able to image calcium signals in deep brain region such as LA and distinguish subpopulations of neurons in separate colour channels. Based on previously reported miniature microscope design (Ghosh et al., 2011), we have created mini-microscopes that image two colour channels simultaneously and is compatible with deep brain imaging.

3-G-167 Multimodal imaging of structural covariance in the mouse brain

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Networks of brain region volume covariances ("structural covariance") are being increasingly used as a means to understand brain development and as biomarkers of disease. Such networks are constructed

by estimating the covariance in volume between each pair of brain regions for a given population. Since volumes are often determined via automated registration-based procedures that depend on the input image contrasts, questions on the robustness of structural covariance networks with respect to imaging modality remain. Here, we construct networks of structural covariance in mice using high resolution (~50 µm) whole brain images of mouse brains. 203 MR images (scanned in house at 7T, T2 weighted) and 489 two-photon autofluorescence images (Allen Institute) were used to construct networks for each imaging modality. Volumes were determined using deformation based morphometry; each group of images was registered independently. We found that networks constructed from the separate modalities were highly similar. Using the two-photon image constructed network as ground truth, the MRI image constructed network predicted true network edges with 88.6% sensitivity and 87.3% specificity. Furthermore, regions that strongly covaried with each other clustered into distinct sets that represent distinct anatomical systems in both networks. These results suggest that structural covariance networks can be robustly constructed from brain images obtained from different modalities.

3-G-168 Direct detection of axonal and somatodendritic release of Arginine Vasopressin by sniffer cells.

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Although mainly synthesized by the paraventricular nucleus (PVN) and the supraoptic nucleus (SON), arginine vasopressin (AVP) is also produced in several other brain regions within and without the hypothalamus. It is involved in many physiological functions such as salt and fluid balance, vasoconstriction, regulation of circadian rhythms, regulation of body temperature, and social behaviour. Due the complexity and variety of processes in which AVP is involved, methods required to study its release in real time are crucial. All the currents protocols available today allow only indirect detection, have low temporal resolution, require expensive equipment, or are complex to implement. In the past, sniffer cells have been used to study the role of oxytocin in rat brainstem autonomic neurones in slice. This has proven to be a powerful and inexpensive method to study direct release of peptides. In this study, we are using HEK 293 cells transfected with the AVP V1a receptor and the calcium indicator GCaMP6m. Following bath application of several concentrations of exogenous AVP (uM to pM) on these cells, we were able to detect AVP induced fluorescence. We then tested the ability of these cells to detect AVP release followed by electrical stimulation from axon terminals of SON and PVN neurones in the posterior pituitary. Finally, we suspended and plated the cells over rat slices containing the SON. We obtained whole-cell current clamp recordings from magnosecretory neurons (MNCs) and we were able to detect somatodendritic release of AVP following stimulation of the MNCs.

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

3-H-169 Neuroscience Findings in Canadian National News: 2000-2015

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With the development of increasingly powerful research methods, our understanding of the brain is advanced on daily basis. Neuroscientific findings have a strong impacts on the society since it is devoted to study the host of human identities. Many neuroscience research have significant implications which are able to transform law and public policy. For instance, neuroscience evidences supporting the

immaturity of juvenile brains subsequently leading to the ban of capital punishment for juveniles in the States (Roper v. Simmons). Accurate translation of research findings into the public domain is challenging. This is compounded by the inclination of the media to use sensational headlines, and the limited amount of time allocated to science in the news: only 1 to 2% of the news topics among media outlets are in science. To investigate how neuroscience findings are interpreted and conveyed to the general public in Canada, articles discussing neuroscientific findings published between January 2000 and December 2015 are screened and analyzed. The analysis is circumscribed to two Canadian national newspapers, National Post, and The Globe and Mail. The articles are categorized into 12 main categories according to the framework devised by O'Connor and colleagues from the University College London. In addition, articles that cited the original sources are put into a separate category. For the articles that cited the original sources, the number of claims and the extent of each claim made in each article compared to the conclusions made in the original sources are analyzed.

3-H-170 The neuroscience classroom 2016: online pedagogical changes to enhance student-focussed learning

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Building upon changes in 3rd year undergraduate neuroscience course content and curriculum as part of the neurobiology program, we sought to bring a greater depth to senior level courses including seminars. Using a variety of online tools that we describe here, we developed online assessments and communication modes to enhance senior level (3rd and 4th year) undergraduate neuroscience program. Purpose: Course re-design was intended to foster an open learning environment in senior level courses using primary paper and research driven content. The re-design sought to refine undergraduate learning outcomes to match post-graduate expectations in neuroscience. These outcomes included independent literature research and critical review, the ability to design key experiments, understand greater depth of material and enhance presentation skills through focussed journal clubs. Lastly, we examined the impact of these changes in a student-centered learning environment through various online assignments and "critical thinking" take-home exams. Methodology: 3 cohorts of senior level students were given various methods of assessment including an online e-book publication, in-class peer reviews of presentations, an integrative writing assignment and a take home examination to provide students with more critical-thinking scenarios based on lectures and independent research. All content was streamed online. Results: Anonymous surveys showed that students felt the re-design aided in better understanding of the material as well as in developing critical thinking skills.

3-H-171 Advertising & Articulating Neuroscience: Human Brain in Performance on Commercial Ads

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The 'neurorevolution', we witness today, transcends the neuroscience labs, research centres and brain institutions. It has indeed become part of our everyday and vernacular culture (de Certeau; Labov). In this regard, the human brain is seen as the protagonist of a neuro-movement and neuroculture (Ortega; Vidal) expressed in our society through the means of popular culture, that is, literature, film, arts and media. Bearing this in mind, this poster investigates contemporary commercials ads that use representations of the brain as the main agent to articulate neuroscience messages. Thus, this study

uses rhetoric and performance as theoretical and methodological approaches (Bauman; Burke; Foss; Goffman; Latour) to analyse the discursive content of the ads in both verbal and non-verbal forms, including audio-visual elements. Moreover, this poster classifies the human brain performed in the selected ads according to neurocognitive functions -- such as decision-making, memory, attention and affect -- as well as neuroscience current theories, for example, plasticity, localization and neuroimaging (Damasio; Doidge; Fitzpatrick; Northoff). Hence, this study argues that the fictional representations of the brain in those commercial ads not only portray the human organ as an iconic sign but also as a 'cerebral self,' participating in a contextualization process in order to create meanings to engage a lay audience within the neuroscience discourse.

IBRO – International Brain Research Organization

3-IBRO-172 ROS Released By Astrocytes in Response to AβOs Affect Neuronal Distribution and Function of pSerStat3

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Astrocytes are essential for neuronal survival; however, under pathological conditions astrocytes participate in the degeneration of adjacent neurons. One of the hallmarks of Alzheimer's disease (AD) is the presence of amyloid-beta oligomers (AβOs) in AD patient's brains. Astrocytes respond to AβOs through a process called reactive astrogliosis, which generates reactive oxygen/nitrogen species (ROS/RNS) and inflammatory cytokines that affect surrounding neurons. Stat3 is a crucial transcription factor involved in maintenance and function of nervous system. Recently, its deregulation has been implicated in AD. In neurons, Stat3 is associated to survival, antioxidant and neuroregenerative responses. Growth factors induce serine-727 phosphorylation and this modification associates with the modulation of transcriptional Stat3 activity. Methods: Primary hippocampal neurons and astrocytes were used. Changes in pSerStat3 distribution were detected by ICC. The oxidative tone and ROS production were evaluated by fluorescent maleimides and H2-DCF assays, respectively. Finally, PCR was used to detect Bcl2 and Bax mRNA levels. Results: Here, we show that conditioned media, derived from astrocytes treated with AβOs (ACM-AβOs), induced the redistribution of pSerStat3 from the nuclei to the cytoplasm. In addition, ACM-AβOs increased neuronal oxidative tone and the Bax/Bcl2 ratio. Conclusion: We propose that in hippocampal neurons, pSerStat3 is a redox sensor for astrocyte-produced ROS induced by AβOs activation and that this astrocyte-derived redox signal could facilitate apoptotic death.

3-IBRO-173 Downregulation of autophagy attenuates axonal degeneration after traumatic lesion to the central nervous system.

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Traumatic lesions to the central nervous system (CNS) usually result in permanent deficits. The understanding of mechanisms involved in degenerative events in the CNS is pivotal for the development of novel therapeutic strategies. Autophagy is a cellular degradation process responsible for the turnover of proteins and organelles. Recently, we demonstrated that autophagy is increased in degenerating axons after spinal cord lesion. Therefore, autophagy might be an important mechanism regulating axonal degeneration following traumatic lesion and its inhibition could be promising in order to block

axonal degeneration. Thus, we generated adeno-associated viral vectors expressing a dominant-negative form of ULK1 (ULK1.DN), a key protein involved in autophagy induction, to decrease autophagy specifically in neurons and study the role of autophagy in axonal degeneration in vitro and in vivo. We show here that moderate decrease of autophagy by overexpression of ULK1.DN in primary cortical neurons cultured in a microfluidic chamber decreases axonal degeneration after axotomy. Moreover, overexpression of ULK1.DN in retinal ganglion cells attenuates axonal degeneration of the proximal axons after optic nerve crush assessed by in vivo live imaging. Finally, overexpression of ULK1.DN in rubrospinal neurons protects the proximal axons from degeneration after spinal cord injury. Taken together, our data provides a new strategy to stabilize lesioned axons after traumatic lesion to the CNS and characterizes ULK1 as a specific therapeutic target for traumatic and neurodegenerative disorders.

3-IBRO-174 Involvement of proteasome in Aβ oligomers-induced synaptic dysfunction

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Synaptic loss is a key pathophysiological feature of Alzheimer's disease (DA) 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. As cellular protein levels vary as a function of synthesis and degradation, dysfunction in any of those mechanisms could explain selective reduction on synaptic protein levels. Here, we have investigated the activity of the proteasome, the main degration machinery in the cell, in experimental models of AD. We found that Aβ oligomers (AβOs), increasingly recognized as proximal synaptotoxins in AD, trigger inhibition of proteasome activity in activity in (1) isolated neuronal synaptosomes, (2) primary cultures of hippocampal neurons, and (3) in synaptosomes isolated from the hippocampi of mice that received an intracerebroventricular injection of AβOs. Comparison between results obtained in whole neuronal homogenates and in isolated synaptosomes indicates that proteasome inhibition is particularly evident on synapses. We further found, that pharmacological proteasome inhibition by lactacystin, induces a reduction in denditic spine numbers density in hippocampal neurons and occludes the reduction in spines induced by AβOs. This suggests that spine elimination induced by lactacystin and AβOs share a common mechamism. Previous studies indicate that proteasome inhibition leads to reduced protein synthesis by the accumulation of translational repressors. Consistent with this notion, w

3-IBRO-175 Retinal Neuroprotective effects of A2a receptor antagonist SCH58261

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Light induced retinal degeneration (LIRD) resembles retinal degenerative diseases and is a useful model to search for neuroprotective strategies. The modulation of adenosine A2a receptors has proved to be neuroprotective in other retinal injuries and in CNS pathologies. The aim of this work was to evaluate the potential protective effect of A2a antagonists. Sprague Dawley rats were intravitreally injected in one eye with SCH 58261 and contralateral eyes with vehicle. Then, rats were submitted to either continuous illumination (12000 lux) or the regular illumination cycle (12hs:12hs; 80lux) for 1 day. Eyes were processed by immunocytochemistry (ICC), TUNEL or western blot (WB). Primary antibodies against GFAP (DAKO) and activated caspase 3 (C3a; Sigma) were used. GFAP immunoreactive areas and number of positive TUNEL cells were quantified. Data was analysed using Student´s t test. Animals treated with

SCH 58261 show a diminution in GFAP expression confirmed by WB and ICC (P< 0.01 and P=0.0001; respectively). C3a levels measured by WB show a lower expression in the treated eyes (P=0.0005), while TUNEL shows also a trend indicating lower number of apoptotic cells. Our results suggest that the activation of MCs is controlled at least partially by A2a. A2a antagonism has shown to diminish glial reactivity in our model. Additionally, our current results show a lower level of apoptosis, currently being confirmed. Globally, SCH 58261 seems to have a neuroprotective effect that needs further studies to become an effective therapy in retinal degenerative diseases.

3-IBRO-176 Long term effects of early-ethanol exposure on the developing rat brain: A proteomic study.

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The mechanisms behind the persistent effects of early alcohol exposure are largely unknown. Alcohol exposure may alter the developing neurons and glial cells by modifying the expression or functionality of proteins. This study aimed to explore the long-term effects of early-ethanol exposure on proteins in the brain. Male Sprague-Dawley rat pups were exposed to 12 % ethanol (4 g/kg/day i.p.) or volume controlled saline from postnatal day (P) 4 - P9 which is considered to be equivalent to the third trimester of human pregnancy. On P31, the prefrontal cortex (PFC) and dorsal hippocampus (DH) were removed for proteomic analysis by iTRAQ labelling and quantification by liquid chromatography mass spectrometry. A fold change >2 identified differentially expressed proteins and a fold change >1.2 in the same direction indicated a supporting trend. Early-ethanol exposure down-regulated energy metabolism-related proteins such as ATP synthase (subunit g) and glycogen synthase kinase-3β in the DH. This result was supported by a decrease in ATP synthase (subunits alpha, beta and gamma), ATP synthase F(0) complex subunit B1, cyctochrome c oxidase (subunits 5B and 7C), the mitochondrial phosphate transporter, SLC25A3, acetyl-CoA acetyltransferase, acetyltransferase component of pyruvate dehydrogenase, aldehyde dehydrogenase, and 2-oxoglutarate dehydrogenase. This decreased capacity for ATP production was not observed in the PFC. The data suggests that early-alcohol exposure results in differential long-term alterations in energy metabolism-related protein expression in the brain.

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