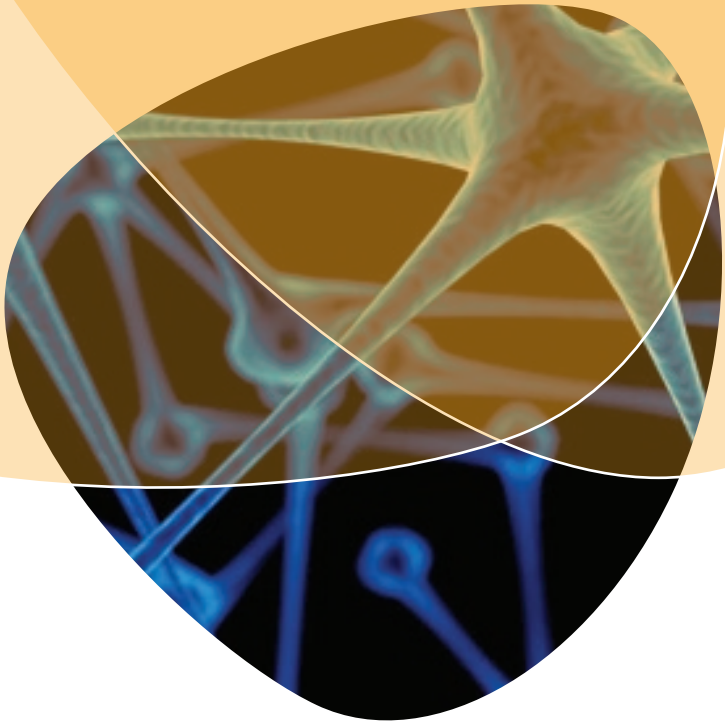
The Canadian Association
for Neuroscience presents

7th Annual Canadian Neuroscience Meeting 2013



CAN-ACN Posters

Authors, Titles, Affiliations & Abstracts, Sessions 1, 2 & 3

May 21–24, 2013

Sheraton Centre Toronto Hotel
Toronto, Ontario

www.can-acn.org

Poster Session 1

A - Development

1-A-1 Development Of Bimanual Coordination In Young Athletes: Sex- And Experience-Related Effects

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Development of bimanual coordination in young athletes: sex- and experience-related effects. David Albines, L.E. Sergio Sch. Kinesiol. Health Sci, York Univ., Toronto, ON, Canada Differences in bimanual coordination have been found in both skilled performance and in the underlying brain activity patterns. Sex-based differences in neural connectivity and the elite-level athlete's extensive performance experience would seem to account for these differences. There has been limited study of the interplay between sex, experience, and age in bimanual coordination development. We characterize performance in relation to age, sex, and athletic experience to gain insight into the neural processes that underlie this advanced level of eye-hand coordination using a novel bimanual visuomotor task. We studied two age/experience groups: adolescent (10-14 year olds, select vs house league athletes) and young adult (17-23 year olds, NHL/NWHL/varsity vs recreational athletes). We observed significant main effects of both athletic experience and sex ($P<0.001$) on task completion time. Comparing experience level within the adolescent group, there was no significant difference as a function of experience or sex. There were significant differences found within the young adult group ($P<0.001$). These results show that the effect of skill and sex is not seen until later years developmentally, however at that point there is a strong effect of sex on bimanual coordination. The data suggest that sex-related advantage in bimanual coordination is not innate, taking place only later in development.

1-A-2 Effect of isolation rearing and predator odour stress on measures of startle and dopaminergic D1 and D2 receptor levels in the prefrontal cortex of male and female rats

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The purpose of our work is to examine the effects of adolescent stress exposure on prefrontal cortex (PFC) function by examining pre-pulse inhibition (PPI), startle amplitude (SA) and dopamine receptor levels, which change throughout adolescence in the PFC, and therefore may be targets of stress during this developmental period. Our previous work established that repeated predator odour stress during adolescence does not significantly affect these measures or associated dopaminergic prefrontal D1R and D2R levels in either sex (unpublished data). In the present study, Long-Evans rats of both sexes were given a combination of isolation rearing and repeated predator odour stress to determine if the removal of the social support offered by a cagemate could result in reducing the animals' resilience to odour stress. Animals were isolated for most of the adolescent period (PND28-54); six odour exposures were given during this period (on PND34, 38, 43, 47,53 and 69). Measures of SA and PPI were assessed repeatedly throughout adolescence and early adulthood; in addition, the levels of dopamine D1 and D2 receptors were measured in the medial PFC and caudate-putamen after the final odour exposure. Preliminary analysis of the data has revealed a reduction in PPI following exposure to a combination of isolation and predator odour exposure. Females showed a transient effect of stress that emerged during adolescence itself, while among males, stress reduced PPI only after the final exposure in early adulthood. This work was supported by a Discovery Grant (NSERC) to Tara Perrot.

1-A-3 ERP evidence for temporal pitch perception in infancy

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Pitch extraction is thought to depend on both spectral cues arising from lower harmonics that are resolved by cochlear filters in the inner ear, and on temporal cues arising from the pattern of action potentials contained in the cochlear output. Adults extract pitch in the absence of robust spectral cues, taking advantage of the temporal cues that remain. However, behavioural evidence suggests that infants have difficulty discriminating between stimuli with different pitches when resolvable spectral cues are absent. In Experiment 1, the mismatch negativity (MMN) component is used to examine cortical pitch discrimination for iterated rippled noise (IRN) stimuli in 4- and 8-month-old infants. IRN stimuli are pitch-evoking sounds generated from repeatedly adding a segment of white noise to itself at a constant delay. IRN stimuli with pitches of 200 and 167 Hz (delays of 5 and 6 ms, respectively) were created and highpass filtered to remove all resolvable spectral pitch cues. No evidence was found that infants could detect the change in the pitch of these IRN stimuli. In Experiment 2, infants were first exposed to a brief period of pitch-priming during which a sine wave was added to the IRN stimulus at its perceived pitch. Following this priming, infants showed a significant MMN to pitch changes in the IRN stimuli with sine waves removed. This suggests that (1) infants can use temporal cues to process pitch, although such processing is not mature and (2) that a short amount of pitch priming experience can alter pitch representations in auditory cortex during infancy.

1-A-4 Calcium-Sensing Receptor And Integrin Protein Complexes In The Developing Cerebellum

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The calcium-sensing receptor (CaSR) is a G-protein coupled receptor related to the mGluRs. It exerts its effects by sensing changes in extracellular calcium levels. The role of the CaSR in CNS development is not well understood. We have shown that in medullary-thyroid cancer cells, the CaSR promotes cell migration via coupling to the integrin family of extracellular-matrix binding proteins (Tharmalingam et al., 2011). The goal of our current work is to determine whether the CaSR and integrins are present in a signaling complex in the CNS, and to study the role of this complex in neuronal migration. We have discovered that in the developing rat cerebellum, a robust but transient increase in CaSR expression, and that the CaSR and β1 integrins are present in a protein complex. We have also identified abundant CaSR-β1 integrin co-localization in the external granule-cell layer (EGL) of the cerebellum. The EGL contains granule-cell precursor neurons (GCP) that proliferate and migrate into the inner granule-cell layer. GCPs proliferate aberrantly in medulloblastoma, a common form of childhood brain cancer. We observed that stimulation of the CaSR results in increased migration of GCPs towards an extracellular-matrix gradient and increased proliferation of GCPs in organotypic cerebellar slices. Our preliminary results suggest that the CaSR-β1 integrin complex may be involved in the proliferation and migration of GCPs. Our findings suggest that manipulation of this complex may be relevant to the study of medullobastomas.

1-A-5 Compartmentation of Lysosomal Acid Phosphatase 2 (Acp2) expression in the mouse cerebellar cortex

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The Acp2 gene encodes lysosomal acid phosphatase 2 (ACP2), an isoenzyme that hydrolyzes orthophosphoric monoesters to alcohol and phosphate. Mutations in this gene compromise lysosomal function and cause acid phosphatase deficiency. Loss of Acp2 in brain causes defects in the cerebellum. Here, we performed an in depth protein expression analysis in the mouse cerebellum to understand how Acp2 controls cellular function in the developing and adult brain. We have found that during development, ACP2 expression marks that caudal midbrain and

cerebellum, two regions that are linked by multiple signaling mechanisms during embryogenesis. By around P8, ACP2 was localized predominantly to the somata of Purkinje cells, the principal neurons of the cerebellar cortex. During the second postnatal week, we found that ACP2 expression expanded into the dendrites and axon terminals of Purkinje cells. However, at two weeks of age only a subset of Purkinje cells strongly express ACP2. Further expression analyses revealed that in the mature cerebellum ACP2 expression divided Purkinje cells into a pattern of molecular zones that are associated with the functional topography of sensory-motor circuitry. These data suggest that ACP2 expression is dynamically regulated during development, and in the adult it may function within a complex architecture that is linked to cerebellar modular organization. Thus, our data provides the first clues into how lysosomal enzyme function may control circuit development and brain behavior.

1-A-6 Vertebrate Intersectin1 is repurposed to facilitate cortical midline connectivity and higher order cognition

Ameet Sengar[1], **Jacob Ellegood**[2], **Adelaide Yiu**[1], **Sheena Josselyn**[1], **R Mark Henkelman**[2], **Michael Salter**[1], **Sean Egan**[1]
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Mammalian Intersectin1 (Itsn1), an adapter protein involved in synaptic morphology and vesicle recycling, can undergo alternative splicing to include DBL/PH and C2 domains not present in invertebrate Itsn proteins. To probe for specific functions of vertebrate Itsn1, we generated Itsn1 mutant mice. Diffusion tensor imaging and tractography of mutant mouse brains reveal intercortical tracts - corpus callosum, ventral hippocampal and anterior commissures - failed to cross the medial longitudinal fissure in mice lacking Itsn1. In contrast, the cerebral peduncle, a cortical-originating tract that crosses the midline within the brainstem, was unaffected. Likewise Itsn1 mutants did not differ from WT animals in non-cortical tracts such as cerebellar peduncle, trigeminal cranial nerve and optic tract. Itsn1 mutant mice showed severe deficits in Morris water maze and contextual fear memory tasks and in bimanual coordination which requires an intact corpus callosum. Thus, coincident with the acquisition of additional signaling domains, vertebrate Itsn1 has been functionally repurposed to facilitate interhemispheric connectivity essential for high order cognitive functions.

1-A-7 Activity Dependent Plasticity in AMPAR composition at a Developing Central Synapse

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[1]Hospital for Sick Children

Development of high fidelity neurotransmission at the calyx of Held synapse requires a postsynaptic switch of slow-gating GluA1 dominant to fast-gating GluA4 dominant AMPARs, but the signal mechanisms remain unknown. The coincidence of hearing onset with the AMPAR gating switch suggests activity dependent mechanisms may drive this change. To test this, we stimulate developing synapses (P7-10) with patterned trains mimicking sound evoked activity. When MNTB neurons were held in the cell-attached mode before rupturing the membrane to establish whole-cell recording, we found that this stimulation accelerates the fast decay constant (tau-f) of evoked EPSCs(eEPSC). Distribution histograms of mEPSC tau-f values for naive and stimulated synapses show 2 populations of mEPSCs with tau-f being 0.4 and 0.7ms, respectively, with the relative weight of the fast population increased in stimulated synapses. These changes are blocked by NMDAR or mGluR antagonism, translation inhibition and inhibitors of CaMK and PKC signalling which are implicated in AMPAR regulation. Application of a peptide which out competes an interaction between "Neuronal Activity Regulated Pentraxin"(Narp), and AMPARs, blocks this gating switch, supporting a role for pentraxins in the activity dependent remodeling of this synapse. Finally, these kinetic changes are absent in GluR4KO synapses, suggesting GluR4 is an indispensable substrate underlying this switch.

These results implicate sensory activity works through NMDARs/mGluRs and downstream signalling mechanisms to mediate AMPAR subunit switching at this synapse.

1-A-8 Role of the precursor form of the brain-derived neurotrophic factor, proBDNF, on GABAergic synapse maturation in neocortex

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Basket cells innervate hundreds of postsynaptic targets with synapses clustered around the soma and proximal dendrites. They are important for gamma oscillation generation and for the regulation of developmental cortical plasticity. Although the function of basket cells within cortical networks is being explored, the mechanisms that control the development of their extensive arborisation and synaptic contacts have not been entirely resolved. BDNF has been shown to be a strong modulator of activity-dependent maturation of GABAergic synapses. BDNF is initially synthesized as a precursor, proBDNF, which is cleaved to produce mature BDNF. Whether proBDNF per se plays a role in the development of basket cell synaptic territory is unknown. Our results show that treating organotypic cultures prepared from mouse cortex during the synaptic proliferation phase with exogenous cleavage-resistant proBDNF strongly reduces the synaptic territory of basket cells. To increase endogenous levels of proBDNF, we treated cultures with a tPA-inactivating peptide, PPACK, which also reduces basket cell synaptic innervation. We further tested whether the neurotrophin receptor p75 plays a role in the maturation of basket cells; by employing REX, a p75 function-blocking antibody, and by causing a basket cell specific KO of p75. In both these conditions, basket cells form exuberant perisomatic and global innervations compared to control cells. All together, these results suggest that proBDNF negatively regulates the synaptic territory of basket cells through direct activation of its p75 receptor.

1-A-9 Status epilepticus-induced precocious expression of KCC2 impairs excitatory synapse formation

Patricia Awad[1]**, Bidisha Chattopadhyaya**[1]**, Joanna Szczurkowska**[2]**, Nathalie Sanon**[1]**, Elie Baho**[1]**, Sandra Duss**[1]**, Sébastien Desgent**[1]**, Laura Cancedda**[2]**, Lionel Carmant**[1]**, Graziella Di Cristo**[1]
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[2]Italian Institute of Technology (IIT)

Febrile seizures affect 5% of children. About 2% will develop atypical febrile seizures with an increased risk of developing epilepsy. The presence of a cerebral malformation (cortical dysplasia) predisposes to the development of both atypical hyperthermic seizures and temporal lobe epilepsy. We have established a rodent model of dual pathology by combining a cortical freeze lesion at post-natal day 1(P1) and hyperthermia-induced seizure at P10 (LH rats). We showed that 86% of LH males develop epilepsy and learning and memory deficits in adulthood. The goal of this study is to determine whether and how alterations in KCC2 function before the onset of spontaneous seizures are involved in spine alterations in LH model. KCC2 is a cotransporter that is crucial for assisting GABA responses undergo a switch from excitatory in the developing brain to inhibitory in the adult. My preliminary data show an increase of KCC2 expression exclusively in LH rats, as well as a hyperpolarization of the reversal potential of GABA. We also observed a striking reduction in spine density in CA1 pyramidal neurons and a reduction of mEPSC amplitude and frequency. Interestingly, KCC2 has already been implicated in spine development; we therefore mimicked the overexpression of KCC2 in hippocampal organotypic culture by biolistic transfection and by in utero electroporation. Manipulations of KCC2 levels decrease spine density and spine maturity. Determining the role of KCC2 in spine development may help us understand the mechanisms underlying memory and learning deficits in atypical febrile seizure.

1-A-203 Role of the transcription factor Lmx1b in the development of Lamina I projection neurons and the relay of pain sensation

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[1]IRCM Montreal, [2]McGill University

Pain is sensed by dorsal root ganglia neurons that relay sensory information to Lamina I projection neurons in the spinal cord. These projection neurons extend axons to different nuclei in the brain, which are involved in the processing of the sensory information, which is then perceived as pain. Surprisingly, the molecular identity, the specific brain targets of these projection neurons, and their relative contribution to pain sensation is poorly understood. We therefore aim to characterize the molecular identity and axonal projections of Lamina I neurons, and ablate them using genetic means. The transcription factor Lmx1b is essential for dorsal horn development and human Lmx1b mutations cause, among others, nociception defects. To label dorsal horn projection axons and identify their brain targets, we generated Lmx1b:Cre; Rosa26:lox:tdTomato:lox:GFP mice in which we detect GFP-expressing axons in the Parabrachial Nucleus (Pb) and the Periaqueductal Grey (PAG). Furthermore, we demonstrate that Lmx1b mutant mice show an absence of the projection neuron marker Neurokinin 1 Receptor in Lamina I and reduced innervation of the Pb and PAG, suggesting that Lmx1b is necessary for the development of Lamina I projection neurons and the innervation of these nuclei. To assess the behavioral consequences of deleting Lmx1b in the spinal cord, we generated conditional Lmx1b knockout mice, which show robust defects in mechanical and inflammatory nociception tests. These experiments provide us with insights into the role of Lmx1b in the formation of the nociceptive neuronal circuitry.

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

1-B-10 Calcium-dependent regulation electrical coupling between bag cell neurons of Aplysia

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Synchronous firing between neurons is often essential to control fundamental physiological behaviors. The bag cell neurons of Aplysia californica are a group of electrically coupled neurons that generate a synchronous burst, known as the afterdischarge, to secret hormones and initiate reproduction. The afterdischarge starts with a fast phase of 5 Hz for 1 min, followed by a slow phase of 1 Hz for 30 min, and is accompanied by elevated Ca2 due to influx and release. Electrical synapses or gap junctions promote this synchronized activity between essentially all bag cell neurons. Here, we examined the nature of electrical coupling between paired bag cell neurons in primary culture using tight-seal, dual whole-cell recording. Junctional conductance was independent of transjunctional and postsynaptic voltage. Coupling coefficient became larger as the junctional conductance increased. The gap junction blockers, meclofenamic and niflumic acid, but not glycyrrhetinic acid and quinine, considerably attenuated coupling. Ca2 influx, produced by delivering a 1-min train of depolarizing pulses at 5 or 1 Hz, suppressed the junctional conductance in comparison to control. These findings suggest that bag cell neurons gap junctions are voltage-independent and the coupling coefficient is strongly related to junctional conductance. Our data shows that coupling coefficient is insensitive to small junctional conductance changes, but inhibition of the electrical synapse by elevated Ca2 during the afterdischarge will increase input resistance and significantly impact excitability.

1-B-11 The Cav3-Kv4 complex acts as a calcium sensor to adaptively modulate inhibitory network function during repetitive excitatory input

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Synaptic transmission and neuronal excitability depends on the concentration of extracellular calcium ([Ca]o), yet repetitive synaptic input is known to decrease [Ca]o in numerous brain regions. In the cerebellar molecular layer, synaptic input reduces [Ca]o by up to 0.4 mM in the vicinity of stellate cell interneurons and Purkinje cell dendrites. The mechanisms used to maintain network excitability and Purkinje cell output in the face of this rapid change in calcium gradient have remained an enigma. Here we use single and dual patch recordings in an in vitro rat slice preparation to determine the effects of physiological decreases in [Ca]o on the excitability of cerebellar stellate cells and their inhibitory regulation of Purkinje cells. We find that a Cav3-Kv4 ion channel complex expressed in stellate cells acts as a calcium sensor that responds to a decrease in [Ca]o by dynamically adjusting stellate cell output to maintain inhibitory charge transfer to Purkinje cells. The Cav3-Kv4 complex thus enables an adaptive regulation of inhibitory input to Purkinje cells during fluctuations in [Ca]o, providing a homeostatic control mechanism to regulate Purkinje cell excitability during repetitive afferent activity.

1-B-12 Norepinephrine Induces Metaplasticity By Recruiting Translation And Transcription: Electrophysiological And Polysomal Profile Analyses

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Synapses in the nervous system are modified by neuromodulatory transmitters, such as norepinephrine (NE). Such modifications are believed to importantly contribute to behavioral learning and long-term memory. Here, we show that application of NE can boost LTP at hippocampal CA3-CA1 synapses. This enhancement of LTP lasts for at least 4 hours and requires β-adrenergic receptor activation, protein synthesis, and transcription. In the CA1 region of mouse hippocampus, a 15-min application of NE prior to LTP induction induces a metaplastic form of LTP similar to that elicited when NE was applied overlapping with high-frequency stimulation; both conditions induced potentiation significantly greater than that observed with tetanus alone. NE metaplasticity was unaffected by inhibition of NR2A subunit-containing NMDA receptors. Additionally, NE metaplasticity was unaffected by inhibitors of histone acetyltransferase and Epac. We have also initiated polysomal profiling of hippocampal tissue extracts, in an attempt to objectively identify which transcripts are preferentially translated following NE-induced enhancement of LTP in area CA1. Polysome profiling coupled with RT-qPCR of gradient fractions is a proxy for assessing translational efficiency of a given mRNA. This entails the monitoring of shifts in the abundance of a given mRNA as measured with RT-qPCR in polysome versus monosome gradient fractions. These studies will shed light on how β-adrenergic receptor activation by NE recruits the translation of particular transcripts. Funded by CIHR.

1-B-13 Delta-catenin is palmitoylated following fear conditioning, and is essential for activity-dependent enhancements of synapse structure and efficacy

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Cadherin adhesion molecules are known to be essential players in mediating activity-dependent changes in synapse structure and plasticity. However, it is unclear how fluctuations in neuronal activity translate to changes in cadherin-based adhesion at the synapse. Here we demonstrate that activity increases the palmitoylation of δ-catenin, a brain-specific component of the cadherin adhesion complex, and enhances its recruitment to synapses and its binding to N-cadherin. Palmitoylation of δ-catenin as well as its its binding to cadherin are essential for activity-mediated stabilization of cadherin at the synaptic membrane. Furthermore, palmitoylation of δ-catenin and its binding to

cadherin are essential for activity-induced remodeling of synapse structure and the insertion of AMPA receptors into the synaptic membrane. Importantly, palmitoylation of δ-catenin and δ-catenin/cadherin interactions are dramatically increased in the hippocampus following fear conditioning. We propose that palmitoylated δ-catenin coordinates activity-dependent changes in synapse adhesion, structure, and efficacy that are important for memory formation.

1-B-14 An LRRTM4-HSPG Complex Mediates Excitatory Synapse Development on Dentate Gyrus Granule Cells

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Formation of complex neuronal networks in the brain require selective synapse development in distinct pathways and cell types. Postsynaptic neuroligins and LRRTMs bind across the synaptic cleft to presynaptic neurexins and widely mediate excitatory synapse development. Alterations in these gene families increase the risk of developing psychiatric disorders. Unlike LRRTM2, we report that LRRTM4 has a distinct presynaptic binding partner, the heparan sulphate proteoglycans (HSPGs), notably glypicans. HSPGs are essential for mediating the synaptogenic activity of LRRTM4. LRRTM4 expression in the brain is regionally restricted; within the hippocampus we detected LRRTM4 exclusively in the dentate gyrus granule cells. LRRTM4 -/- dentate granule cells but not CA1 pyramidal cells exhibit selective reductions in excitatory synapse density and function. Furthermore, activity regulated AMPA receptor trafficking was impaired in the dentate gyrus granule cells of LRRTM4 -/- mice. These results identifying cell type-specific functions and distinct presynaptic binding partners for LRRTMs reveal an unexpected complexity in the design of synapse organizing complexes.

1-B-15 Roles of non-Smad signaling pathways and secretory leukocyte protease inhibitor in regulating TGF beta-induced expression of neurocan

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Axonal regeneration after spinal cord injury is inhibited by chondroitin sulphate proteoglycans (CSPGs) such as neurocan, which are expressed in the glial scar. Neurocan expression can be induced by transforming growth factor β (TGFβ), which suggests that inhibiting TGFβ signaling may reduce neurocan levels following injury. A recent study from our laboratory showed that elevation of cyclic AMP (cAMP) could reduce levels of the TGFβ signaling protein Smad2 in neurons, and we have now found that cAMP significantly reduces Smad2 levels in astrocytes. However, when cAMP-treated astrocytes were exposed to TGFβ, neurocan expression was still strongly induced, which suggests that TGFβ may mediate neurocan expression through non-Smad pathways. To test this hypothesis, astrocytes were first incubated with either Smad2 or Smad4 siRNA, and then treated with TGFβ. TGFβ-induced neurocan expression was still observed in the absence of Smad2 or Smad4, indicating that Smad signaling is not required for neurocan expression. When astrocytes were treated with inhibitors of either the PI3K-Akt or Erk pathways, we observed significant reductions in neurocan, which suggests that these pathways are responsible for mediating neurocan expression. In addition, we have found that astrocytes from mice lacking expression of secretory leukocyte protease inhibitor (SLPI) have significantly lower levels of neurocan compared to wild type astrocytes. Targeting non-Smad signaling pathways and SLPI may therefore be effective strategies to reduce neurocan expression following spinal cord injury.

1-B-16 Mitochondrial metabolism regulates the strength of synaptic inhibition by uncovering silent GABAergic synapses

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Reactive oxygen species (ROS) are ubiquitous signaling molecules in the CNS primarily formed as by-products from mitochondrial metabolism. During periods of increased metabolism, mitochondrial ROS (mROS) generation is up-regulated. This is of particular physiological relevance in the context of synaptic function where elevated ROS levels may modulate synaptic neurotransmission. As the major inhibitory neurotransmission system in the brain, the GABAergic system has developed the sensitivity to react to constantly changing neuronal environments. Accordingly, we set out to uncover the influence of mitochondrial metabolism on the GABAergic system. Using patch-clamp recordings and mitochondrial poisons to elevate mROS, we observed a rapid increase in cerebellar interneuron GABAergic small amplitude, slow decaying miniature inhibitory postsynaptic currents (mIPSCs). The significance of mitochondrial stress in modulating GABAergic transmission was confirmed using the Fenton reaction and/or an antioxidant. Finally, in an attempt to elucidate the molecular basis for observed changes in GABAergic mIPSCs we used mutant α1- and α3-KO mice and identified the importance of α3-containing GABA-A receptors for this phenomenon. Taken together, our data identify a novel regulatory mechanism in which GABAergic transmission is modulated in a subunit-specific manner under the control of mROS. Our data suggests functionally active neurons may possess fast-acting compensatory mechanisms to down-regulate neuronal excitability by enhancing inhibition during periods of increased metabolic activity.

1-B-17 Short-term plasticity encoded within voltage-gated potassium channels at a central synapse

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Central neurons encode information in bursts of action potentials (APs/spikes), but little is known about the gating behavior of voltage-gated ion channels during repetitive spike firing. We discover that when evoked by a pair or short burst of APs, currents mediated by voltage-gated potassium channels (Kvs) at a central nerve terminal facilitate in a frequency and voltage-dependent, but surprisingly Ca2 -independent manner. This facilitation originates from dynamic transition of intermediate gating states of Kvs, and specifically attenuates spike amplitude and inter-spike potential during burst firing at high rates. Computer simulations and paired voltage-clamp recordings from pre- and postsynaptic elements further demonstrate that facilitation of presynaptic Kvs dramatically regulates the magnitude and polarity of short-term plasticity in Ca2 currents and transmitter release, which enhances postsynaptic spiking fidelity. We conclude that activity-dependent facilitation of Kvs enables an unexpected form of plasticity to impart central synapses with a feed-forward gain control of information transfer.

1-B-18 Visualization of dynamic cAMP in dendritic spines during synaptic plasticity

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Understanding how synaptic function is modulated by neural activity is essential for elucidating the mechanisms of learning and memory. Here we study the role of cAMP, a ubiquitous second messenger, in synaptic plasticity. cAMP is a major second messenger and essential for regulating a wide variety of cellular events. The cAMP signaling cascade in neurons is involved in synaptic plasticity (such as in late-phase LTP), however, little is known about its activity-dependent dynamics at the individual synapse level in living neurons. Combining a genetically encoded fluorescence protein-based FRET (Förster resonance energy

transfer) /FLIM (fluorescence lifetime imaging microscopy) probe and 2-photon laser scanning microscopy, we have visualized the spatio-temporal dynamics of cAMP in living neurons using cultured organotypic hippocampal slices. CaMKII (calcium/calmodulin-dependent protein kinase type II) is a critical enzymatic protein which triggers synaptic plasticity. To compare cAMP dynamics and CaMKII activity in synaptic plasticity, we combined cAMP FRET/FLIM probes and CaMKII FRET/FLIM probes to simultaneously monitor both signaling cascades in living neurons. For a deeper understanding of cAMP function, techniques to directly manipulate cAMP levels are required. Combining a new optogenetic approach and 2-photon microscopy, we have established a light-dependent local cAMP production and imaging technique for use in living neurons. Using these genetically engineered molecules and 2-photon imaging techniques, we will discuss the role of cAMP in synaptic plasticity.

1-B-19 Regulation of presynaptic calcium in short- and long-term plasticity of cortical inputs to the dorsolateral striatum

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The dorsal striatum is essential for the formation of habits and motor skills, and these forms of learning are hypothesized to involve plasticity at striatal synapses. Cortical inputs to the dorsolateral striatum (DLS) exhibit various forms of plasticity that manifest as short- or long-term depression (STD, LTD) of glutamate release. Despite the presynaptic locus of expression of corticostriatal STD and LTD, their presynaptic mechanisms remain largely unexplored. We developed a novel approach to detecting presynaptic calcium (Ca2) influx in cortical terminals in the DLS, and used it to probe the involvement of presynaptic Ca2 in corticostriatal plasticity. Following Cre-dependent viral expression of the genetically encoded Ca2 indicator GCaMP5 in cortical projection neurons of Emx1-Cre mice, we used fluorescence photometry to record, in slice, electrically evoked presynaptic Ca2 transients (preCaTs) within the DLS. Tetrodotoxin-sensitive Na channels and cadmium-sensitive voltage-gated Ca2 channels were required to evoke preCaTs. Application of the GABAB agonist baclofen induced STD of both preCaTs and striatal field potentials. Studies are currently underway to assess the role of presynaptic Ca2 influx in endocannabinoid- and serotonin-mediated corticostriatal LTD. These findings provide new insight into the presynaptic mechanisms of corticostriatal plasticity that may contribute to striatal-dependent learning.

1-B-20 Experimentally constrained network models of hippocampal fast-firing parvalbumin-positive interneurons

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The fast-firing properties of parvalbumin-positive (PV) interneurons, and their extensive connections with excitatory neurons, provide them with enormous potential to influence network rhythms. Currently, direct links between fast-spiking interneuron models and empirically determined cellular intrinsic and network properties are unclear, and so model predictions can be difficult to interpret in a biological setting. Thus, we created a network model of PV interneurons that is tied to experimental work on multiple levels, and we investigated its potential to realize coherent oscillations.P/Whole-cell patch clamp recordings of fast-spiking PV interneurons in the CA1 of an intact hippocampus in vitro were used to derive cellular properties, from which we constrained a mathematical model. Our network model is composed of these PV cell models, and we determined network size, connectivity, and synaptic properties to be consistent with our analysis of PV activity during an emergent network rhythm, as well as those from the literature.P/ Our model

produced spiking characteristics and firing behaviors which approximated those determined experimentally. Simulations of our network model produced coherent fast gamma firing (80-180 Hz), but only within parameter ranges that minimally overlap those determined experimentally. Specifically, PV-PV inhibitory synaptic conductance must be very small, whereas external excitatory inputs must be quite large. Thus, our work indicates that CA1 PV networks may produce fast population rhythms, but can be easily perturbed out of this state.

1-B-21 Electrical field stimulation enhances cortico-hippocampal communication during the neocortical slow oscillation

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The signature event of slow-wave sleep (SWS) is the neocortical large amplitude slow oscillation (SO; ~1Hz) that is composed of alternating periods of highly active (UP) and silent (DOWN) states at the neuronal level. On each wave, the SO is generated at a local focus in the neocortex, and is propagated across the cortical network, and even to the hippocampus, in various directional patterns. This potential interaction between the neocortex and hippocampus make the SO a favourable candidate for mediating sleep-dependent declarative memory consolidation. In fact, it has been previously shown that the application of transcranial electrical stimulation at the SO frequency to human subjects during SWS improved declarative memory recall the following day. However, the underlying spatiotemporal SO dynamics that may be mediating memory consolidation during sleep and the influence of electrical stimulation on these mechanisms remain elusive. Here, we show in urethane anesthetized rats that rhythmic electrical field stimulation entrains cortical and hippocampal local field and cellular activity and biases the spontaneous propagation of the SO. Field stimulation also enhances long-range gamma synchrony across both cortico-cortical and cortico-hippocampal regions, a potential mechanism for supporting spike-time-dependent plasticity during sleep. These results shed new insights into the potential neurophysiological mechanisms supporting plastic processes during SWS.

1-B-22 Glycine primes depression of NMDA receptor-mediated synaptic transmission in CA1 hippocampus

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NMDAR channel gating is elicited upon simultaneous binding of co-agonists glycine and glutamate to the GluN1 and GluN2 subunits, respectively. We reported previously stimulating the glycine site of NMDARs initiates signaling through the NMDAR complex, priming the receptors for dynamin-dependent endocytosis(Nature 2003). NMDARs in acutely isolated neurons are primarily somatic from the previous study, and here we investigated whether glycine might also prime NMDARs at hippocampal synapses. We treated hippocampal slices with glycine (200 µM in ECS, 5 min) and found that there was a progressive decline of NMDAR-mediated EPSCs: by 30 min after the end of glycine application NMDAR-EPSCs had decreased to 60.2 ± 12.7% of baseline (n = 9 cells), while AMPAR-mediated EPSCs were not affected. D-serine (60 µM), the endogenous agonist of the glycine site of the NMDARs, also produced a progressive decline of NMDAR EPSCs to a similar level (n=6 cells). Glycine treatment led to depression of NMDAR EPSCs that was consistent at holding potentials of -60 mV (n = 8 cells), -10 mV (n = 9 cells) or +40 mV (n = 4 cells), and therefore glycine-primed depression is not voltage-dependent. We found that NMDAR EPSCs did not decline after glycine treatment when dynasore (50 µM), a cell-permeable small molecule inhibitor of dynamin, was applied intracellular through the recording pipette (n= 4 cells). Our findings collectively suggest that NMDARs at synapses in the hippocampus may be primed for internalization by glycine, leading to depression of NMDAR synaptic transmission.

1-B-23 The Dorsal Root Ganglion Sandwich Synapse: Novel Transglial Signaling Between Neuronal Somata

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The dorsal root ganglion contains a subset of closely-apposed neuronal somata (NS) that are separated solely by a thin satellite glial cell (SGC) membrane septum to form a cell trimer. We recently reported that stimulation of one NS evokes a delayed, noisy and long-duration inward current in both itself and its passive partner that was blocked by suramin. Here we test the hypothesis that NS-NS transmission involves purinergic activation of the SGC and its release of an excitatory transmitter. Stimulation of the NS triggered a sustained current noise in the SGC. Block of transmission by reactive blue 2 or thapsigargin implicated a Ca2 store discharge-linked P2Y receptor. P2Y2 was identified by simulation of NGlN-like transmission by puff of UTP onto the SGC. Block of the UTP effect by BAPTA supported the involvement of SGC Ca2 stores in the pathway. The response to UTP was also blocked by AP5, which, along with the NR2B subunit antagonist ifenprodil, inhibited NS-NS transmission, implicating glutamatergic signaling via postsynaptic NMDA receptors. Puff of glutamate could evoke transmission-like current in the NS. Immunocytochemistry localized NR2B to the NS membrane, abutting staining for P2Y2 on the SGC septum. We infer that NS-NS transmission involves secretion of ATP from the NS, SGC Ca2 store discharge via P2Y2 receptors and release of glutamate to activate NS postsynaptic NMDA receptors. Thus, the cells communicate via a Sandwich Synapse transglial pathway, a novel signaling mechanism that may contribute to information transfer in other regions of the nervous system.

1-B-24 Investigating the mechanism of action of AMPA receptor auxiliary proteins

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The AMPA type of ionotropic glutamate receptor carries out the majority of the rapid excitatory synaptic transmission in the central nervous system. Synaptic AMPA receptors are accompanied by numerous auxiliary proteins which alter their trafficking, gating and pharmacology. The prototypical auxiliary protein is stargazin, a member of the transmembrane AMPA receptor regulatory protein (TARP) family. Stargazin increases the efficacy of partial agonists, increases the probability of larger single channel openings and slows deactivation. Stargazin may achieve these effects either by promoting ligand-induced cleft closure of the ligand binding domain (LBD) or by enhancing the coupling between conformational changes in the LBD and the pore. To distinguish between these, we examined the gating of mutant AMPA receptors with destabilized LBDs and asked if stargazin can rescue their gating behaviours. We found that indeed stargazin rescues gating in these mutants as measured by the ratio of glutamate to quisqualate and the distribution of single channel conductances, suggesting that TARPs act in part by stabilizing the LBD. To further test this hypothesis, we used FRET to directly measure the extent of cleft closure in AMPA receptors alone or with stargazin. We found that the presence of stargazin leads to an increased extent of cleft closure with both glutamate and kainate as well as in the apo state. Taken together, our data provide evidence that TARPs enhance AMPA gating by increasing the extent of LBD cleft closure.

1-B-25 Characterization of a Novel Calmodulin Binding Short Linear Motif in an Invertebrate L-type Channel

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ABSTRACT: Voltage gated calcium channels (CaVs) have important roles in several physiological

processes, including muscle contraction, endocrine function, hearing, vision and neurotransmission [1]. They are intimately self-regulated by Ca2 ions via the signal transducing Ca2 binding protein, calmodulin (CaM). CaM is thought to constitutively associate with L-type CaVs at their C-termini in vivo [2-4] and promote rapid channel inactivation upon binding Ca2 , termed calcium dependent inactivation (CDI). Another site found at the N-terminus of L-type channels, a sequence called NSCaTE (N-terminal Spatial Calcium Transforming Element) was also shown to bind CaM, although its precise role in CDI is unclear. NSCaTE fits the definition of a short linear motif (SLiM), and as we show here, is widely conserved in most animal phyla. We have characterized a new NSCaTE sequence from Lymnaea stagnalis (pond snail), which is quite different from the mammalian NSCaTE originally described by Yue and colleagues [5]. Nonetheless, this different (and first ever to be described in invertebrates) NSCaTE binds CaM with comparable affinity and has a modest attenuating effect on Ca2 currents in its native channel (LCaV1), but only under low intracellular buffering conditions (0.5mM EGTA). We propose that the weak and likely transient modulatory binding of CaM to NSCaTE serves to fine-tune the CDI of L-type channels in crucial physiological circumstances such as cardiac muscle contraction.

1-B-26 A uniquely adaptable pore is consistent with NALCN being an ion sensor

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NALCN is an intriguing, orphan ion channel amongst the 4x6 TM family of related voltage gated cation channels that lacks much of the variation that provides the diverse palate of gating features, and tissue specific adaptations of traditional channels. NALCN's most distinctive feature is that that it possesses a highly adaptable pore that is a calcium-like EEEE selectivity filter in radially symmetrical animals, and a more sodium-like EEKE or EKEE selectivity filter in bilaterally symmetrical animals including vertebrates. Two lineages of animals evolved alternative calcium-like EEEE and sodium-like EEKE / EKEE pores, spliced to regulate NALCN functions in differing cellular environments. A highly adaptable pore in an otherwise conserved ion channel in the 4x6TM channel family is not consistent with a role for NALCN in directly gating a significant ion conductance. Appearance of NALCN with a calcium or sodium pore correlates with the relative density of calcium- and sodium-containing fluxes in animals from sponges to humans, and also in different tissues of animals where alternative sodium and calcium pores are available. We suggest that NALCN function as a sensor for the much larger UNC80/UNC79 complex, in a manner consistent with the coupling mechanism known for other weakly or non-conducting 4x6TM channel sensor proteins such as Nax or Cav1.1. We propose that NALCN serves as a variable sensor that responds to calcium or sodium ion flux, depending on whether the total cellular current density is generated more from calcium-selective or sodium-selective channels.

1-B-27 Potentiation of muscarinic excitation by Na+/Ca2+ exchange in prefrontal cortex of the healthy and psychiatrically vulnerable brain

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Acetylcholine (ACh) activation of the prefrontal cortex by muscarinic M1 receptors is essential for executive function, yet the neuronal mechanisms underlying their excitatory effects remain unclear. These Gq-protein coupled receptors trigger the release of calcium (Ca2) ions from internal stores and a prolonged inward current at resting membrane potentials. Here, we used multiphoton Ca2 imaging together with whole-cell electrophysiology to investigate the question of whether Ca2 clearance through electrogenic Na / Ca2 exchangers contributes to the excitatory effects of ACh. Somatic Ca2 increases predicted larger excitatory muscarinic currents, and depletion of Ca2 stores reduced these inward currents. The peak

of the ACh-elicited inward currents was coincident with the clearance of Ca2 , could be extended by additional release of intracellular Ca2 , and could be suppressed by the Na /Ca2 exchange inhibitor K-BR9743. Further experiments tested the sensitivity of ACh-elicited Ca2 increases and their clearance to ionic manipulations of Na and K concentrations. All together, these findings suggest a role for the electrogenic Na -dependent Ca2 exchanger (NCX) and the Na - and K -dependent Ca2 exchanger (NCKX) families in the cholinergic excitation of healthy adult prefrontal cortex. Ongoing work is assessing how this phenomenon is altered in an animal model of psychiatric vulnerability.

1-B-28 Extracellular ion binding distinguishes between AMPA and kainate receptor activation and desensitization

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Ionotropic glutamate receptors mediate much of the fast synaptic transmission that occurs in the CNS. Although AMPA and kainate receptors (AMPARs and KARs) are both capable of rapid activation, KARs make a smaller contribution to postsynaptic currents, and serve primarily as modulators of transmission. We used single channel recordings and molecular dynamics (MD) simulations to test whether any intrinsic properties of KAR activation set them apart from AMPARs, accounting for their divergent roles. Channels comprised of the KAR subunit GluK2 desensitized within milliseconds of glutamate exposure, while the mutation D776K prevented desensitization. MD simulations run using this mutant suggest the amino group on Lys 776 reliably replaces a sodium ion, which is normally bound at the extracellular ligand-binding domain. In the absence of external ions, wildtype GluK2 failed to activate, however GluK2 D776K retained function, suggesting that occupancy of the sodium binding pockets is necessary for KAR activation, while KAR desensitization can only occur upon ion unbinding. Accordingly, other GluK2 mutants shown by MD analysis to disrupt sodium binding were nonfunctional, despite surface expression. Moreover, in AMPARs, which lack such ion modulation, desensitization shortened the duration of activation. Thus, the unique role for bound ions to sustain KAR activation and prevent desensitization leaves open the possibility that auxiliary proteins may alter ion affinity to shape KAR responses. This source of modulation could explain why KARs have different functions than AMPARs.

1-B-29 Presynaptic NMDA Receptors May Contribute to Retinal Ganglion Cell Function and Arbor Formation in Xenopus laevis

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The NMDA-type glutamate receptor has been intensely studied due to its importance in activity-dependent plasticity mechanisms underlying learning and memory formation. More recent experiments have brought unanticipated reports of NMDA receptor expression on presynaptic, as well as postsynaptic terminals. These presynaptic NMDA receptors (preNMDARs) have been found to modulate transmitter release and are essential for several forms of plasticity. Using live imaging and whole cell electrophysiology in the Xenopus laevis tadpole visual system, we found that NMDARs may be present presynaptically on the axon terminals of the Retinal Ganglion Cells (RGCs) that project to tectal cells in the brain. Pharmacological blockade of NMDARs reduces unitary AMPAR EPSC frequency in tectal cells, indicating that preNMDARs may be present on their inputs. Preliminary results from RGC-targeted GluN1 knock-down using an antisense morpholino oligonucleotide indicate that loss of NMDARs causes RGCs to form unusually simple arbors that grow little over time and accumulate few new branches, despite relatively high rates of dynamic branch motility and normal synapse density. These data point to a fundamental role for preNMDARs in retinotectal axon refinement and functional neurotransmission Supported by NSERC

CGS-D (VH), NSERC Banting Fellowship (MRVH), and a grant from CIHR (ESR).

1-B-30 Hydrogen Sulfide influences the excitability of subfornical organ neurons

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Hydrogen sulfide (H2S), a well-known toxic gas, has recently been shown to have beneficial physiological effects on blood pressure and cardiovascular function, and is suspected to act as a signalling molecule in the brain. Our previous microarray analyses have found that cystathionine β-synthase (CBS), an enzyme responsible for the production of H2S, is expressed in the subfornical organ (SFO). This study was thus undertaken to investigate whether the SFO, a central nervous system site well known for regulation of blood pressure and cardiovascular function, may be a site of action of H2S. We used whole-cell patch clamp recordings to investigate the influence of NaHS (an H2S donor) on the membrane potential of SFO neurons. Approximately 96% (46 of 48) of neurons tested showed a response to H2S. Of the neurons tested with H2S (10 µM), 100% (28 of 28) showed a fast acting, short lasting depolarization with a mean magnitude of 21.0 ± 0.3 mV. Of the neurons tested with H2S (1 µM), 89% (20 of 22) responded, showing a temporally similar depolarization with a mean magnitude of 13.9 ± 0.3 mV. This study has demonstrated that H2S has the ability to change the membrane potential of SFO neurons, and is therefore the first to identify the SFO as a potential site of action of H2S Supported by the Canadian Institutes of Health Research.

1-B-31 Role of the Synaptotagmin-Dynamin interaction in synaptic vesicle recycling

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Synaptic vesicle protein Synaptotagmin I (Syt I) is a well-studied calcium sensor critical for synchronized neurotransmitter release. However, the role of the highly conserved Syt I juxtamembrane domain has yet to be investigated. Using pulldown assays with fusion proteins, we have shown that the Syt I juxtamembrane region directly interacts with the endocytic protein Dynamin. The interaction is specific to the Dynamin I isoform and is localized to its membrane-interacting pleckstrin homology domain. Notably, this interaction is blocked in vitro by mutation of a conserved Syt I phosphorylation site. We hypothesize that this interaction mediates activity-dependent retrieval of synaptic vesicles, and thus may influence short-term synaptic plasticity. Imaging experiments with dissociated cultures of hippocampal neurons with lentiviral-mediated expression of non-interacting mutant Syt I are being conducted to determine if blocking the interaction affects endocytosis. Data from pulse-chase experiments using the exogenous membrane tracer FM 4-64 to assay the rate of endocytosis will be presented. These findings have implications in uncovering a molecular link between synaptic vesicle exocytosis and endocytosis.

1-B-32 Pannexin 1 regulates ventricular zone neural stem and progenitor cell behaviours and forms a novel interaction with collapsin response mediator protein 2

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Pannexins are large-pore channels permeable to ions and metabolites of up to 1 kDa in size. We previously detected pannexin 1 (Panx1) expression in ventricular zone neural stem and progenitor cells, and demonstrated a role for this channel in the positive regulation of neural stem and progenitor cell proliferation, acting at least in part through release of adenosine triphosphate (ATP). Furthermore, our more recent data indicates Panx1 is involved in maintaining these cells within the cell cycle, and blocking this channel causes G1 phase stall and cell cycle exit leading to neuronal differentiation. To further understand the mechanism by which Panx1 regulates these cell

behaviours, we used an unbiased proteomic approach to identify putative protein interaction partners. We found a novel interaction with collapsin response mediator protein 2 (Crmp2), a cytoskeletal-associated phospho-protein up-regulated early in neurogenesis. Additionally, Crmp2 plays a role in neurite outgrowth and neuronal maturation. Therefore we hypothesize that this newly identified interaction between Panx1 and Crmp2 represents an additional mechanism through which Panx1 regulates neural stem and progenitor cell behaviours. Furthermore, as Crmp2 has been previously implicated in several disorders of the nervous system, including Alzheimer's disease, these novel findings have important implications for neurogenesis within both the healthy and injured brain.

1-B-33 Dendritic calcium nonlinearities switch the direction of synaptic plasticity in fast-spiking interneurons

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In fast-spiking parvalbumin-positive interneurons, action potentials (APs) attenuate largely with distance from the soma because of the non-uniform distribution of voltage-gated ion conductances. Moreover, an AP-evoked calcium signal is not required for the induction of some forms of synaptic plasticity. Supralinear calcium events initiated in distal dendrites of different cell types can play a role in the induction of synaptic plasticity. However, the mechanisms and roles of these events in interneurons remain unknown. Here, we combined whole-cell patch-clamp recordings and two-photon calcium imaging to study the mechanisms of local calcium nonlinearities evoked in distal dendrites of hippocampal CA1 fast-spiking cells by local bipolar stimulation. Postsynaptic calcium transients (CaTs) exhibited nonlinear summation and were mediated by the activation of ionotropic glutamate receptors. Blocking calcium-permeable AMPA receptors resulted in a complete block of supralinear CaTs, while blocking NMDA receptors had a small effect on the CaT summation. Moreover, blocking L- or T-type calcium channels had no effect on CaT summation whereas blocking calcium release from internal stores led to a linear summation of CaTs. Finally, supralinear CaTs were involved in controlling the direction of plasticity at interneuron excitatory synapses. Taken together, our data reveals a new form of regenerative activity generated by synchronous activation of distal dendritic inputs and resulting from the calcium-induced calcium release that plays a role in the regulation of synaptic plasticity.

1-B-34 Group 1 metabotropic glutamate receptors play a role in the pathogenesis of beta amyloid in Alzheimer's disease

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The peptide beta amyloid (Aβ) is one of the main contributors to the neurodegeneration that characterises Alzheimer's disease (AD). Evidence suggests that of the Aβ oligomers, the Aβ42 fragment exerts the most potent neurotoxic effects. Although a number of receptors have been proposed as the binding site for Aβ42, the precise receptor to which Aβ42 binds remains unclear. Implicated in Aβ42 neurotoxicity are the group 1 metabotropic glutamate receptors mGluR1 and 5. Research shows that these receptors may act as extracellular scaffolds for Aβ42 oligomer binding, leading to altered group 1 mGluR signalling and trafficking. Here we show that cell surface expression of mGluR5 is elevated in the APPswe/PS1ΔE9 mice mouse model of AD while the knock out mGluR5 in these mice causes a 50% reduction in the formation of Aβ42 oligomers and plaques. Additionally, knock out of mGluR5 in these mice was found to rescue spatial memory in the Morris water maze task. Although group 1 mGluR mediated signalling is unaffected in APPswe/PS1ΔE9, we believe that damage to these receptors, disassociation with Gαq may occur and/or group 1 mGluRs play a role in the processing

of APP. This data provides us with insight into how group 1 mGluRs are altered in AD and may provide us with a novel strategy with which to treat altered glutamatergic signalling in neurodegenerative diseases such as AD.

1-B-35 Characterization of invertebrate sodium-selective (Nav1) and calcium-selective (Nav2) voltage-gated sodium channels

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Our laboratory is examining the invertebrate voltage-gated sodium channel genes, Nav1 and Nav2 from the pond snail, Lymnaea stagnalis. The snail, LNav1 sodium channel is the only gene in the snail genome representing the ten different human voltage-gated sodium channels, which include Nav1.1 to Nav1.9 and salt sensor Nax. Surprisingly, we have found that the LNav1 channel transcript is restricted to the snail brain. We have cloned the full length LNav1 channel cDNA for in vitro expression in HEK-293T cells. The full length mRNA of LNav1 is 6345 bp in length, coding for 2115 amino acids. The snail sodium channel has highly conserved DEKA selectivity filter and sequences for a fast inactivation gate, and likely serves as the sodium channel for action potential generation in the snail. We are also isolating the invertebrate-specific voltage-gated sodium channel, Nav2, which is has a DEEA calcium selectivity filter, and is permeable to calcium ions. Nav2 mRNA is undetectable in every tissue except sensory neurons, such as in eyes and tentacles. Our laboratory is especially interested in the promiscuous ion selectivity in 4x6TM channels, which includes voltage-gated sodium and calcium channels and NALCN. Snails have a calcium-selective sodium channel (Nav2), a sodium-permeant T-type calcium channel, and a NALCN channel with both calcium and sodium (EKEE) sensing pores. Detailed analyses of these variable channel pores, provides insights into the features that govern sodium and calcium selectivity.

1-B-36 Characterization of a microglial-specific BDNF-deficient mouse

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Mice with targeted deletion of microglial BDNF were generated from cd11b-cre and floxed BDNF mice (cd11b-cre /loxP-BDNF / experimental animals; cd11b-cre-/loxP-BDNF / controls). This resulted in the deletion of BDNF from myeloid cells and specifically from microglia within the CNS. The pain phenotype of these mice was investigated using the spared nerve injury model (SNI) to induce neuropathic pain and Complete Freund's Adjuvant (CFA) to induce inflammatory pain in separate animals. Behavioural responses were quantified by measuring withdrawal thresholds to mechanical stimulation. ATP-induced calcium transients were imaged using adult microglial cultures. Basal nociceptive thresholds were equal in cd11b-cre /loxP-BDNF / and controls. SNI induced hypersensitivity in controls but in cd11b-cre /loxP-BDNF / mice thresholds remained unchanged from baseline and higher than controls ($p<0.001$). Spinal microgliosis was indistinguishable between groups. Following CFA-induced inflammation both cd11b-cre /loxP-BDNF / and control animals exhibited equivalent oedema and hypersensitivity. Expression and function of P2X4 receptors were unchanged in cd11b-cre /loxP-BDNF / mice. However, no BDNF expression was evident in cultured cd11b-cre /loxP-BDNF / microglia following ATP stimulation. Mice with targeted deletion of microglial BDNF show normal nociceptive thresholds and microglial proliferation following SNI. However pain behaviour associated with neuropathy, but not inflammation, was absent.

1-B-37 Metallothionein 2 directly activates the ion channel TRPA1 and contributes to inflammatory pain

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Pain is initiated by activation of noxious stimulus-responsive ion channel receptors present on the peripheral terminals of nociceptor sensory neurons, transducing intense mechanical, thermal and chemical stimuli into ion fluxes. Although inflammatory mediators can sensitize ion channels in nociceptors by post-translational changes following activation of intracellular signaling pathways through their cognate receptors, no endogenous protein is known to activate ion channels directly. We now show that metallothionein (MT) 2, but not its closely-related isoform MT1, directly activates the transient receptor potential (TRP) A1 cation channel by binding to its extracellular face. Such activation is quite unlike known TRPA1 agonists, which form covalent bonds with intracellular N-terminal domain cysteine and lysine residues. MT2 preferentially activates TRPA1-expressing nociceptors, an effect lost in TRPA1-deficient mice. Structural analysis of MT2 shows similarities with bivalent tarantula toxins that act directly on TRPV1. Intraplantar injection of MT2 evokes acute nocifensive behavior and produces hypersensitivity to mechanical and cold stimuli. Peripheral inflammation results in MT2 induction, and it is secreted upon stimulation of fibroblasts and macrophages with interleukin-1β. Inflammatory pain is reduced in MT1/2 null mice and in wildtype mice treated with an anti-MT1/2 antibody. We conclude that MT2 is an endogenous protein TRPA1 ligand that contributes to inflammatory pain.

1-B-38 The zebrafish Danio rerio expresses two Pannexin 1 ohnologs in the retina

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Pannexin 1, a large pore channel protein, is expressed in the inner and outer retina of higher vertebrates. In the inner retina, genetic ablation of Panx1 in mice reduces post-ischemic neurotoxicity in retinal ganglion cells, whereas in the outer retina the mediation of feedback from horizontal cells (HCs) to photoreceptors is discussed as a potential physiological function of Panx1. In zebrafish, we initially identified exclusive expression of zebrafish Panx1 (drPanx1a) at HC dendrites, invaginating deeply into the cone pedicle. Here, we present the non-overlapping expression of a second Panx1 protein, drPanx1b, in the ganglion cell and inner nuclear layer in the fish retina, solving the inconsistency of retinal Panx1 expression in higher vertebrate retinae. The functional comparison of the evolutionary distant drPanx1 ohnologs revealed conserved and unique properties. When exogenously expressed in Neuroblastoma 2a cells, both proteins form channels opening at resting membrane potential, which get regulated by intracellular calcium, extracellular ATP and pH. Both proteins are glycosylated, with drPanx1b displaying an unusual and complex glycosylation pattern. Both proteins form voltage-gated channels that differ significantly in their gating kinetics. Our findings led us conclude that both drPanx1 proteins may fulfill different functions in vivo. These two natural variants found in the inner and outer fish retina provide the unique opportunity to investigate central functions of Panx1 in the processing of visual information. Funding: CRC/CIHR, NSERC-DG (G.Z.)

1-B-39 Cholinergic excitation of layer VI neurons in cortex is strongly dependent on cortical region

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Nicotinic acetylcholine α4β2* receptors in layer VI of medial prefrontal cortex play a key role in mediating normal attentional performance. Additionally, the deep layers of many other cortical regions also contain these nicotinic receptor subunits as well as muscarinic acetylcholine receptors. However, neither the extent nor the nature of layer VI neuronal responses to acetylcholine have been contrasted across multiple cortical regions. Here, we investigated the responses to acetylcholine in layer VI neurons of three cortical regions (medial prefrontal cortex, mPFC; primary motor cortex, M1; and primary

somatosensory cortex, SSC) using whole cell recording in acute brain slices. Acetylcholine elicited excitatory responses in layer VI neurons of all three cortical regions, with significantly greater effects in mPFC. Both nicotinic and muscarinic receptors contributed to the cortical cholinergic responses, with strongly region-dependent differences in the balance between these components. Pharmacological dissection of acetylcholine responses across regions showed a large and dominant α4β2* nicotinic receptor response in mPFC, but only a minor excitatory muscarinic component. In contrast, smaller acetylcholine responses in M1 and SSC were more balanced between their nicotinic and muscarinic components. These results highlight the unique status of layer VI neurons of mPFC in terms of their strong excitatory response to acetylcholine and their dependence on nicotinic acetylcholine receptors. Support: CIHR Grant MOP 89825 (EKL)

1-B-40 Cholesterol is Required for Actin-Dependent Clustering of Synaptic Vesicle Proteins during Endocytosis

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Synaptic vesicles (SVs) and their proteins must be recycled for sustained synaptic transmission to occur. Here we tested the hypothesis that the high cholesterol content of SV membrane is required for proper sorting of SV proteins during sustained exocytosis and endocytosis. We used the reversible block of endocytosis in the Drosophila temperature-sensitive dynamin mutant, shibire-ts1 (shi), to trap both SVs and their proteins on the plasma membrane. When exocytosed SVs were trapped on the plasma membrane we used methyl-β-cyclodextrin, (MβCD), a cholesterol chelator, to extract vesicular cholesterol. The clustering of SV proteins seen during endocytic blockade was prevented by vesicular cholesterol extraction. Given that SV proteins and actin colocalize, we tested whether actin was required to cluster SV proteins trapped on the plasma membrane. Application of Latrunculin A (LatA) to disrupt actin after SVs and their proteins had been trapped on the plasma membrane resulted in loss of SV protein clustering. LatA also prevented recovery of synaptic transmission in shi mutants due to impaired SV endocytosis, demonstrated by reduced FM1-43 uptake. In addition, we found that vesicular cholesterol regulates actin clustering. Cholesterol is thought to regulate actin dynamics through PIP2. We found that clustering of PIP2 was reduced following extraction of vesicular cholesterol. Our results demonstrate that vesicular cholesterol is important for PIP2 and actin aggregation, which in turn are responsible for the clustering and sorting of SV proteins during SV recycling.

1-B-41 Interaction with the microtubule network facilitates plasticity of the Cx36 nexus

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Electrical synapses, -the gap junctions of the nervous system-, have been viewed for decades as passive intercellular conduits, lacking use-dependent plasticity. More recently, activities of the protein kinases CaMKII and PKA were correlated with morphological and electrophysiological plasticity, providing a molecular link between neuronal activity and strength of connection at this type of synapse. However, these kinases represent only a "bookend" of a complex molecular machinery enabling neuronal dendrites to process and receive information by utilizing both electrical and chemical communication. Here, we provide experimental evidence that Cx36, the major neuronal gap junction protein found in a majority of electrical synapses in the CNS, interacts with the microtubule network by binding to tubulin. We identified the tubulin binding site and confirmed direct interaction by CoIP, Surface Plasmon Resonance Technology and Microtubule Binding Assays in vitro and in vivo. In transfected N2a cells, we found that Cx36/tubulin interaction is critical for ,,runup,"

using an established double patch clamp protocol eliciting a plasticity response of electrical synapses. Finally, Live Cell Imaging and TIRF microscopy were used to confirm that transport of Cx36 depends on interaction with the microtubule network. From our results, we conclude that the strength of transmission at electrical synapses is dependent on orchestrated transport and interaction with regulatory proteins such as CaMKII or PKA. Our study sheds further insight into the molecular dynamics of the Cx36 nexus.

1-B-42 The Role of CAV2.2 C-Terminus In Calcium Channel Anchoring At The Presynaptic Transmitter Release Sites

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Voltage gated neuronal calcium channels (Cav2.2) gate neurotransmitter release at specialized regions within the presynaptic nerve terminals, known as transmitter release sites (TRS). Studies have predicted that calcium channels are closely attached to the TRS in an organized structure, supporting a channel-channel anchoring mechanism. Although calcium channels have been linked to a broad range of presynaptic proteins, molecular components of the channel-channel anchor are poorly understood. Our objective is to identify the mechanism of Ca channel anchoring at the TRS and will explore the role of channel cytoplasmic regions. GST or strep tagged Cav2.2 cytoplasmic region fusion proteins were used for pull-down assays from which distal C-terminus region (C3strep) captured the channel from brain lysate. In order to determine the specific region responsible for Cav2.2 capture, GST fusion proteins comprising overlapping proximal (C3proximal) and distal (C3distal) regions of C3strep were generated. Our data show that C3distal region pulls down the channel from avian synaptosome membrane lysate. This finding was supported by a reduction of channel capture from brain lysate in the presence of a blocking peptide mimicking the last four amino acids of long splice variant Cav2.2 distal C-terminus which code a PDZ-ligand domain. C3strep protein was also able to pull-down transfected Cav2.2 from tsA201 cell lysate, narrowing down possibilities of a channel-channel bridging protein(s). Overall, these data suggest a key role for Cav2.2 distal C-terminus in channel anchoring at TRS.

1-B-43 Synaptic Vesicle Capture by Intact CaV2.2 Channels

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The fusion of synaptic vesicles (SVs) at the presynaptic transmitter release face is gated by Ca2 influx from nearby voltage gated calcium channels (CaV). Our early functional studies argued that the CaV and SV are linked by a molecular anchor or 'tether' and recent studies have proposed a direct cytoplasmic link to the channel distal C terminal. In order to explore CaV-SV binding we developed an in vitro assay, termed SV-PD, to test for capture of purified, intact SVs. Antibody-immobilized presynaptic or expressed CaV2.2 channels but not plain beads, IgG or pre-blocked antibody successfully captured SVs, as assessed by Western blot for a variety of protein markers. SV-PD was also observed with a distal C terminal fusion protein, C3strep, supporting involvement of this CaV region. Our results favor the model where presynaptic CaV can tether SVs directly, independently of the surface membrane.

1-B-44 Anoxia-mediated NMDA receptor silencing resulting from mitochondrial calcium release through the permeability transition pore in turtle neurons

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Mammalian neurons are anoxia-sensitive and rapidly undergo excitotoxic cell death when deprived of oxygen, mediated largely by calcium entry through over-activation of N-methyl-D-aspartate receptors (NMDARs). This does not occur in neurons of the anoxia-tolerant western painted turtle, where a 47 ± 7% decrease in NMDAR currents is observed after 30 minutes of anoxia.

This decrease is dependent on a modest rise in [Ca2+]c that is mediated by release from a mitochondrial source. The aim of this study was to determine if the mitochondrial permeability transition pore (mPTP) is involved in NMDAR silencing through release of mitochondrial Ca2+. Activation of the mPTP with atractyloside during normoxia resulted in an increase in [Ca2+]c and a 50 ± 9% decrease in NMDAR currents, while mPTP inhibition during anoxia with cyclosporin-A attenuated the rise in [Ca2+]c and abolished the reduction in NMDAR currents. Release of Ca2+ through the mPTP is driven by its electrochemical gradient, as an 8 ± 2% decrease in the mitochondrial membrane potential (Ψm) occurs during anoxia. Inhibition of the F1-F0 ATPase with oligomycin during anoxia resulted in a 5-fold decrease in Ψm, an effect that was replicated by the protonophore FCCP. Collectively, the data indicate that transient mPTP opening following the onset of anoxia decreases NMDAR currents through a release of sequestered mitochondrial Ca2+ in response to a decrease in Ψm and turtle mitochondria avoid a collapse of Ψm during anoxia by hydrolyzing ATP via the F1-F0 ATPase to maintain Ψm at a new depolarized set-point.

1-B-45 Relative changes of intrinsic excitability are sufficient for preferential recruitment of neurons into a fear memory trace

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A fundamental goal of neuroscience is to elucidate mechanisms memories are encoded and stored. Identifying the physical representation of memory within the brain (memory trace) is a long-standing challenge since Lashley's "search for the engram". We've shown that lateral amygdala (LA) neurons with increased CREB are competitively advantaged for recruitment into a fear memory trace. Here, we examined the mechanism underlying this competitive advantage. Given that CREB activity robustly increases neuronal excitability, we examined whether directly manipulating intrinsic excitability alone is sufficient to select neurons for inclusion in the memory trace. To directly manipulate intrinsic excitability in a subset of LA neurons, we infused viral vectors expressing a dominant-negative KCNQ2 channel or DREADD HM3D channel activated by CNO. Intrinsic excitability in ~20% LA neurons enhanced memory in wild-type mice, analogous to previous findings of overexpressing CREB. Further, increasing excitability in LA neurons was sufficient to rescue memory deficit in genetically-engineered mice with targeted disruption of CREB. Our results suggest that eligible neurons are selected in a memory trace as a function of their relative excitability around the time of learning.

1-B-46 GABAA Transmission Regulates Dendritic Spine Formation in the Developing Organotypic Hippocampal Slice

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γ-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the mature nervous system, but remarkably, GABA is depolarizing in immature neurons. During this immature phase, glutamatergic synapses are actively forming and maturing on dendritic spines. To assess whether early GABAergic neurotransmission influences the formation of excitatory synapses, we modulated GABAergic transmission while monitoring dendritic spine formation on CA1 neurons in mouse organotypic hippocampal slices. Similar to previous findings, inhibiting mature GABAA transmission for 48 hours with gabazine (Gbz) or bicuculline in slices grown for 5 days in vitro (DIV) caused robust spine loss. Surprisingly, the same manipulation in younger slices (3 DIV) increased spine density by 33%, while driving GABAA transmission at 3 DIV caused an opposite 25% decrease in spine density. The period over which this switch in the effect of GABAA blockade occurred (3-5DIV) was paralleled by a marked increase in KCC2 expression. Importantly, GABAA blockade did not itself alter KCC2 levels in developing slices. Finally, to investigate whether

GABAA transmission plays a cell autonomous role in spine formation we have developed a TetOn system for turning the expression of a dominant negative γ2 GABAA receptor subunit on and off again in sparse populations of cells in organotypic slices. Together, our findings suggest that GABAA transmission regulates spine formation in early development.

1-B-47 Functional Interplay Between TRP, SK, And N-Type Calcium Channels Regulates Tonic Firing Rate In Rat Paraventricular Thalamic Neurons

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Thalamocortical (TC) neurons in the rat Paraventricular Thalamus (PVT), exhibit both burst and tonic firing, correlating with low and high arousal states, respectively. While the ionic conductances underlying burst firing are well characterized, less is known about those that regulate tonic firing. Current-clamp and two-photon calcium imaging experiments show that PVT TC neurons fire sustained and weakly accommodating trains of action potentials (APs) at current injections <120 pA. This was accompanied by a long lasting (τ~5s) somatic calcium transient and a much shorter duration (τ~1.5s) transient in primary and secondary dendrites. Increasing current injection led to the genesis of depolarization block (DB), with little change in calcium dynamics during DB. DB was calcium-dependent as blockade of N-type Ca2+ channels, or chelating intracellular Ca2+ resulted in DB at low current injections (≤30 pA), and was accompanied by an 80% decrease in the amplitude of the Ca2+ transient. Blockade of transient receptor potential (TRP) channels led to classical spike frequency adaptation rather than sustained trains, and there was little role for intracellular stores or SK potassium channels. Interestingly, blockade of TRP and SK channels together recapitulated the effect of N-type Ca2+ channel block, demonstrating that functional interactions exist between N-type, SK, and TRP channels in these neurons. These interactions regulate the unique tonic firing properties exhibited by TC neurons and have profound implications for information transfer from the PVT to higher brain regions.

1-B-48 CSF2RB, The Beta Receptor Of GM-CSF, Il3 And Il5, Is Expressed By Specialized Spinal Glia Cells And Controls Neuropathic Pain Levels In Mice

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Background and aims: We reported that PAIN1, a locus on mouse chromosome-15, controls autotomy, a neuropathic pain (NP)-related behavior produced by hindpaw denervation. Some evidence implicated Cacng2 as the autotomy gene in PAIN1. But comparing gene expression in spinal cords of high-autotomy A/J ('A') to low-autotomy C57BL6/J ('B') mice identified Csf2rb in PAIN1 as the most robustly upregulated gene post-denervation. Here we validate Csf2rb as another NP gene in PAIN1, and identify cells expressing it. Methods: A and B mice were perfused 14 days post-sciatic/saphenous neurectomy or sham operation. L3-L5 spinal cord (SC) segments were removed, cryo-sectioned and immuno-labeled with CSF2RB and Vimentin (reactive-glia marker). RNA was extracted, reverse-transcribed and underwent qPCR to quantify Csf2rb transcript abundance. Results: Csf2rb mRNA levels were upregulated in autotomizing A mice compared to non-autotomizing or sham A mice, and denervated B mice [2.47±0.33sem vs. 1.20±0.09($p<0.002$), 1.07±0.06($p<0.008$), 1.19±0.05($p<0.004$)]. CSF2RB immunoreactivity, co-localizing with Vimentin, was found in radial glia surrounding the central canal (CC), sending mid-sagittal processes to white matter, more in hindpaw-denervated autotomizing A than B mice [30.23±1.51 vs. 18.13±1.43/50µm section ($p=0.04$)],

and in glia in dorsal columns sending processes to the pia and the dorsal horn. Conclusions: Csf2rb upregulation in the SC by autotomy suggests that it is an additional candidate NP gene in PAIN1, and a GM-CSF/IL3/IL5 receptor associated with NP on CC reactive glia cells.

C – Disorders of the Nervous System

1-C-49 Effects of Deep Brain Stimulation of the Nucleus Accumbens of the Expression and Development of Ethanol Sensitization in Mice

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Dysregulation of the nucleus accumbens (NAc) is thought to contribute to behavioural sensitization the potential of deep brain stimulation (DBS) of the NAc has begun to be explored in addiction-relevant conditions. The present study assessed the effects of NAc DBS on the development and expression of behavioural sensitization to ethanol (EtOH). Male DBA/2 mice received five biweekly injections of EtOH (2.2g/kg, i.p.) or saline (SAL) immediately prior to assessments of locomotor activity (LMA). For some of the mice each EtOH or SAL injection was preceded by 2hr of bilateral NAc DBS, while the remaining mice received no stimulation. Seven days after the last injection LMA was again measured after mice received a challenge dose of EtOH (1.8g/kg, i.p.) or SAL, preceded or not by 2 hr of DBS. Mice receiving NAc DBS before EtOH injections during the sensitization protocol showed progressive increases in LMA that were not different from LMA scores of EtOH injected mice that received no DBS. However, when the latter group was subsequently challenged after receiving DBS, a strong suppression of LMA was observed, in comparison to their own previous LMA scores (-66%) or in comparison to EtOH-sensitized groups challenged in the absence of DBS (-72%). These results suggest that NAc DBS may have different effects at different stages of the EtOH sensitization process, specifically suppressing expression but not the development of EtOH sensitization. Mechanisms underlying these effects merit further investigation, given their potential clinical relevance for treating addictive disorders.

1-C-50 Disruption of a large intergenic non-coding RNA in subjects with neurodevelopmental disabilities

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Large intergenic non-coding (linc) RNAs represent a novel class of ribonucleic acid whose importance in human disease remains undefined. We identified a severely developmentally delayed 16 year-old female with karyotype 46,XX,t(2;11)(p25.1;p15.1)dn in the absence of clinically significant copy number variants (CNVs). DNA capture followed by next-generation sequencing of the translocation breakpoints revealed de novo disruption of a single non-coding gene on chromosome 2, LINC00299, whose RNA product is expressed in all tissues measured, but most abundantly in brain. Among a series of additional, unrelated subjects referred for clinical diagnostic testing who showed CNV affecting this locus, we identified three with exon-crossing deletions in association with neurodevelopmental abnormalities. No disruption of the LINC00299 coding sequence was seen in almost 14,000 control subjects. Together, these subjects with disruption of LINC00299 implicate this particular non-coding RNA in brain development and raise the possibility that, as a class, abnormalities of lincRNAs may play a significant role in human developmental disorders.

1-C-51 In vivo Imaging of Blood-Brain Barrier Disruption in an Animal Model of Multiple Sclerosis

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Multiple sclerosis (MS) is a chronic disease that causes inflammation and demyelination of the central nervous system (CNS). The sequence of events that lead to the formation of white matter lesions is thought to begin with a loss in integrity of the blood-brain barrier (BBB), followed by an infiltration of a large number of immune cells into the CNS from the periphery. The exact timing of these events throughout the course of the disease, as well as the mechanisms involved, are not fully understood. We use an MS animal model, experimental autoimmune encephalomyelitis (EAE) in mice in order to directly image the breakdown of the BBB at various stages of the disease. The integrity of blood vessels in the spinal cord is assessed in vivo using two-photon microscopy of fluorescent markers for vascular permeability. The markers used vary in size in order to find better estimates for the degree of BBB permeability as function of time. We are interested in the correlation between permeability of the BBB, cellular infiltration and demyelination as they relate to the progression of the disease. The study of these biomarkers during the early stages of EAE will help us to better understand the sequence of events that lead to inflammation of the CNS.

1-C-52 Cortical thinning and subcortical white matter changes in Parkinson's disease

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The pathology of Parkinson's disease (PD) involves widespread brain areas beyond the nigrostriatal pathway. The present study investigated structural changes in whole brain of PD using different MRI analysis methods. Specifically, we compared cortical thickness, subcortical gray matter volume, and microstructure of white matter in a group of PD patients with those of a demographically-matched group of healthy controls. Cortical thickness maps and the values of subcortical gray matter volume were derived from T1-weighted images using FreeSurfer. Fractional anisotropy (FA) maps were derived from DWI images using FSL. We also correlated each imaging data with UPDRS scores in the PD group. The PD group showed significant cortical thinning in the left precentral gyrus ($p=0.0199$) and left pericalcarine gyrus ($p=0.0007$), as well as in the right pericalcarine ($p=0.0415$). Negative correlations between cortical thickness and UPDRS scores were found in the left paracentral gyrus ($p=0.0396$), and left superioparietal lobule ($p=0.0014$), as well as in the right postcentral gyrus ($p=0.0001$) and right inferiorparietal lobule ($p=0.0263$). The PD group also showed significantly reduced FA values in several major white matter tracts including Fmaj, Fmin, ILF, IFO, CNG, CST, and SLF ($p< 0.05$) compared with those of the healthy control group. Our data confirm that PD patients have widespread structural brain changes and regional cortical changes are associated with the severity of the disease. How these gray and white matter changes are related needs further investigations.

1-C-53 Potentiation on Quantitative Electroencephalogram Following Prefrontal Repetitive Transcranial Magnetic Stimulation in Major Depression

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The long-lasting effects of repetitive transcranial magnetic stimulation (rTMS) on electroencephalogram (EEG) activity are not clear. We aimed to investigate the cumulative effects of consecutive prefrontal rTMS sessions on EEG and clinical outcomes in major depression. Twenty-five patients with medication-resistant major depression underwent 10 daily rTMS sessions over left dorsolateral prefrontal cortex. Resting EEGs were recorded before and after the rTMS treatment. Spectral power was computed for longitudinal comparisons. Clinical efficacy was

evaluated using Hamilton's Depression Rating Scale (HAM-D) and Wisconsin Card Sorting Test (WCST). In a 3-way ANOVA model, including the midline electrodes, post-hoc analysis indicated significant theta power increase only at Fz (t24 = -2.20, P = 0.038). In an ANOVA model including all prefrontal electrodes, post-hoc analysis revealed significant time effects on theta (F1, 24 = 7.89, P = 0.010; +43%), delta (F1, 24 = 6.58, P = 0.017; +26%), and alpha (F1, 24 = 4.64, P = 0.042; 31%) bands without site specificity. Clinical correlations were observed between alpha power increase by rTMS at F4 and improvement in retardation on HAM-D (ñ = -0.567, P = 0.003, N = 25) and between alpha power increase at F3 and improvement of the absolute changes in the number of perseveration (ñ = -0.687, P < 0.0001, N = 24) and error (ñ = -0.511, P = 0.011, N = 24) on the WCST. Consecutive prefrontal rTMS sessions could induce long-lasting EEG potentiations beyond the aftereffects, possibly associated with improved cognitive and depressive symptoms.

1-C-54 Reorganization of inhibitory synapse innervation in experimental epilepsy

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The integrity of cortical networks is essential for proper brain function. Loss of synaptic stability and organization can lead to disruptions in the excitation/inhibition balance, a characteristic of neurological disorders such as epilepsy. Proper connectivity of the GABAergic network is essential as it provides local inhibitory control that synchronizes brain activity. This study aimed to determine synaptic changes that occurred in the piriform cortex (PC) after kindling-induced seizures. Immunohistochemistry was used to mark perineuronal nets (PNNs: structures in the extracellular matrix that provide synaptic stability and restrict reorganization of inhibitory interneurons) in the PC before and after seizures. Results showed that the overall number of PNNs was significantly reduced following seizures, presumably creating a permissive environment for network rearrangement. qPCR was used to validate the breakdown of PNNs in the PC using genes coding for the proteases, MMP9 and ADAMTS4. These proteases are known to be involved in the degradation of PNNs and showed an increased expression after seizures. Distinct interneurons were then identified by their expression of calcium binding proteins: parvalbumin, calbindin, and calretinin. By co-localizing each calcium binding protein with a presynaptic nerve terminal marker we mapped the interneuron wiring patterns of the PC. Interneuron synaptic nerve terminals were shown to have a significant, layer specific rearrangement after seizures. These studies help to determine changes occurring in the highly plastic PC after seizures.

1-C-55 α9*- and β2*-nicotinic acetylcholine receptors differentially modulate EAE

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Nicotine is a potent inhibitor of the immune response and is protective against experimental autoimmune encephalomyelitis (EAE). Earlier studies suggested that the cholinergic system modulates inflammation via the α7-nicotinic acetylcholine receptor (nAChR) subtype. We recently have shown that effector T cells and myeloid cells constitutively express mRNAs encoding nAChR α9 and β2 subunits and found evidence for immune system roles for non-α7-nAChRs. In the present study, we assessed the effects of nAChR α9 or β2 subunit gene deletion on EAE onset and severity, with or without nicotine treatment. We report again that disease onset is delayed and severity is attenuated in nicotine-treated, wild-type mice, an effect that also is observed in α9 subunit knock-out (KO) mice irrespective of nicotine treatment. On the other hand, β2 KO mice fail to recover from peak measures of disease severity regardless of nicotine treatment, despite retaining sensitivity to nicotine's

attenuation of disease severity. Prior to disease onset, we found significantly less reactive oxygen species production in the CNS of β2 KO mice, elevated proportions of CNS myeloid cells but decreased ratios of CNS macrophages/microglia in α9 or β2 KO mice, and some changes in iNOS, TNF-α and IL-1β mRNA levels in α9 KO and/or β2 KO mice. Our data thus suggest that β2*- and α9*-nAChRs, in addition to α7-nAChRs, play different roles in endogenous and nicotine-dependent modulation of immune functions and could be exploited as therapeutic targets to modulate inflammation and autoimmunity.

1-C-56 Cortical mechanims of mirror activation in Parkinson's disease

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Purpose: To characterize mirror activation (MA) and determine the cortical mechanisms of MA in individuals with Parkinson's disease (PD) that demonstrate mirror movements. Hypothesis: 5Hz rTMS to the supplementary motor area (SMA) will reduce MA by increasing interhemispheric inhibition (IHI) of the ipsilateral motor cortex. Methods: MA was assessed using surface electromyography during maximal and submaximal unimanual contractions of the first dorsal interosseous in 7 individuals with PD with mirror movements (PD-MM: 70.9±13.9 years; UPDRS III: 28.0±8.2), 7 individuals with PD without mirror movements (PD-NM: 71±10.1 years; UPDRS III: 27.8±6.7) and 7 healthy controls (74.4±6.0 years). IHI of the ipsilateral motor cortex was assessed using paired-transcrainal magnetic stimulation. Results: MA was enhanced in both PD groups during submaximal contractions, with the latest onset of activation in PDNM. Ipsilateral motor cortex excitability was the highest in PDMM; however, IHI is reduced in all individuals with PD. 5Hz rTMS to the SMA reduced IHI in PDNM; however, did not affect MA. Conclusions: IHI may not be the sole contributor to the expression of mirror movements in PD. Expression of overt mirror movement may be due to the combination of enhanced ipsilateral motor cortex excitability and a shorter onset of MA in PDMM.

1-C-57 FoxO3a is an important mediator of PARP-1-induced Bnip3 expression and hypoxic mitochondrial toxicity

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The nuclear enzyme poly(ADP-ribose) polymerase-1 (PARP-1) plays a critical role in mitochondrial dysfunction and neuron death in cerebral ischemia, but the mechanisms of PARP-1-induced mitochondrial damage are poorly understood. Bnip3 is a pro-apoptotic protein that causes PARP-1-like mitochondrial dysfunction and can be induced epigenetically by FoxO3a (Forkhead box O 3a). We found previously that PARP-1-induced mitochondrial dysfunction is dependent on Bnip3 expression and that hypoxic Bnip3 expression in cortical neurons is dependent on PARP-1 expression. The central hypothesis of the present study was that PARP-1 controls Bnip3 expression by activating FoxO3a. We used primary cortical neuron cultures exposed to hypoxia. Hypoxia significantly increased Bnip3 mRNA in a manner attenuated by the PARP-1 inhibitor, PJ34, and genetic deletion of PARP-1. Hypoxic PARP-1 activation resulted in reduced intracellular NAD levels and corresponding inhibition of the NAD -dependent class III histone deacetylase, Sirt1. We subsequently demonstrated a direct interaction between Sirt1 and FoxO3a, and that PARP-1 activation leads to FoxO3a acetylation and nuclear translocation in hypoxia. Moreover, chromatin immunoprecipitation revealed PARP-1-dependent hypoxic binding of FoxO3a to the Bnip3 upstream promoter region. FoxO3a silencing using shRNA reduced hypoxic increases in Bnip3 transcription. Taken together, these data demonstrate that hypoxia leads to PARP-1-induced NAD depletion and Sirt1 inhibition, which in turn enhances acetylation of FoxO3a and nuclear Bnip3 promoter activity.

1-C-58 Astrocyte-induced cortical vasodilation is dependent on endothelial nitric oxide synthase

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Astrocytes play a critical role in neurovascular coupling by providing a physical linkage from synapses to arterioles and releasing vaso-active gliotransmitters. We previously identified that astrocyte activation leads to local vasodilation by the gliotransmitter, D-serine and NMDA receptors. We further found that NMDA receptor-mediated vasodilation in isolated brain arteries is dependent on endothelial nitric oxide synthase (eNOS). The objective of this study was to determine whether eNOS is involved in astrocyte-mediated cortical vasodilation. Perivascular astrocytes in mouse cortical slices (20% O2) were activated by bath application of metabotropic glutamate receptor agonist, trans-1,3-dicarboxylic acid (t-ACPD) or flash photolysis of NP-EGTA-loaded astrocytes. Astrocyte Ca2+ and arteriolar lumen diameter were subsequently monitored by two-photon laser scanning microscopy. t-ACPD and flash photolysis both caused astrocyte Ca2+ elevations followed by initiation of local vasodilation. Vasodilatory responses were dramatically reduced by inhibiting eNOS using N5-(1-Iminoethyl)-L-ornithine (L-NIO) or eNOS deletion mice. In addition, the inhibitory effect of L-NIO on vasodilation was mitigated by an inhibitor (HET0016) of the enzyme (ù-hydroxylase) that produces the vasoconstrictor arachidonic acid metabolite, 20-hydroxy arachidonic acid (20-HETE), suggesting that the effect of eNOS requires an active 20-HETE production pathway. Overall, our results show that astrocyte-mediated cortical vasodilation is partly dependent on the eNOS-induced suppression of 20-HETE production.

1-C-59 Does White Cell Count at Presentation have any Implication in Traumatic Brain Injury?

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Does White Cell Count at Presentation have any Implication in Traumatic Brain Injury? Objective: To study the association of high white cell count with severity of head injury and with outcomes in patients with isolated head injury. Methods: It was a retrospective observational study. We reviewed medical charts and electronic database of patients with isolated head injury from 1st January 2006 to 31st June 2012. Demographic variables, Presentation GCS, Revised trauma score and total white cell counts at presentation were recorded. Glasgow outcome scale was then applied on follow up. Data was analyzed on SPSS 19. Results: A total of 121 patients were included in the study. Mean age of our population was 38.86 years (/- 16.71). For the purpose of analysis we divided the population into three groups on the basis of GCS and compared for various variable and mean white cell count. Mean white cell count in mild, moderate and severe head injury was 13.81 ± 6.12, 18.17 ± 5.67, 19.37 ± 7.17 respectively with statistically significant difference between mild and moderate head injury groups (p value < 0.001). We found TLC to be negatively correlated with GCS on arrival with statistical significance (r= - 0.238). However we did not find any significant association with unfavorable outcomes or GOS. Conclusion: Total white cell count is associated with severity of head injury. However study does not find a significant association with outcomes. Studies on larger sample size are required. Key Words: Isolated head injury, Total white cell count, Glasgow outcome scale.

1-C-60 Resveratrol protects dopaminergic cells against high glucose-induced oxidative stress and apoptosis

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Resveratrol (RESV), a natural polyphenolic compound, has long been acknowledged to have cardioprotective, anticarcinogenic and anti-inflammatory actions. RESV holds antioxidant properties reducing the formation of reactive oxygen species (ROS) and leading to oxidative stress and apoptotic death of dopaminergic (DAergic)

neurons, a hallmark of Parkinson's disease (PD). Recent literature has recognized hyperglycemia as a cause of oxidative stress reported to be harmful for the nervous system. In this context, our study aimed a) to evaluate the anti-apoptotic properties of RESV on DAergic cells in a high-glucose condition; b) to study the effect of RESV against high glucose-induced oxidative stress in DAergic neurons. Our results showed that RESV reduces high glucose-induced apoptosis in DAergic cells by modulating DNA fragmentation and the expression of apoptotic markers such as Bax, Bcl-2, p53 and PARP-1. Further results suggested that RESV protects DAergic neurons against high glucose-induced oxidative stress by diminishing levels of ROS. Moreover, RESV rescued expression levels of mortalin, a marker of mitochondria homeostasis known to be implicated in PD, which are significantly decreased by high-glucose treatment. Altogether, our data evoke a correlation between hyperglycemia and neurodegeneration, which provides new insight on the high occurrence of PD in diabetic patients. This study puts forward potent neuroprotective roles for RESV that should be considered as a nutritional recommendation for preventive and/or complementary therapies of neurodegenerative diseases.

1-C-61 Defective autophagy underlies the sensory neuropathy in dystonia musculorum

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Dystonin is a cytoskeletal linker protein whose loss of function in dystonia musculorum mice (dt mice) results in a sensory neuropathy. The autophagic mechanism is reliant upon the cytoskeleton, and is protective in human neurodegenerative diseases. We therefore assessed the influence dystonin loss-of-function imparts on autophagy in the murine nervous system. We initially assessed LC3-II protein levels in sensory neurons across multiple dt alleles (dt27 and dtTg4 mice). We found a significant increase in LC3-II protein levels in pre- and phenotypic sensory neuorns from both dt alleles. In addition, we cultured primary cortical and sensory neurons from pre-phenotype dtTg4 mice and assessed autophagic flux. While no difference in autophagic flux was found between dtTg4 and WT primary cortical neurons, a difference in autophagic flux was observed in dtTg4 primary sensory neurons. As dtTg4 mice are devoid of two major neuronal dystonin-a isoforms (dystonin-a1 and -a2) we addressed which neuronal dystonin isoform was responsible for these aforementioned autophagic defects. We developed dystonin-a2 rescue mice on the dtTg4 background (PrP/PRP/dtTg4). PrP/PRP/dtTg4 sensory neurons showed reduced protein levels of LC3-II, p62, and poly-ubiquitinated proteins compared to dtTg4 sensory neurons, and autophagic flux was reminiscent of WT results. Taken together, defective autophagy underlies dt pathogenesis and dystonin-a2 plays a role in autophagy within sensory neurons. Further investigation will explore the biological mechanism by which dystonin-a2 contributes to autophagy.

1-C-62 Amyloid-beta oligomers disrupt dendritic transport of dense core vesicles through intracellular calcium elevation and calcineurin activation in cultured hippocampal neurons

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Disruption of fast axonal transport (FAT) and intracellular calcium dysregulation are early pathological events in Alzheimer's disease (AD). We have shown that soluble amyloid beta oligomers (AβOs), a causative agent of AD, impede FAT of dense core vesicles by non-excitotoxic activation of calcineurin (CaN), a calcium-dependent phosphatase implicated in AD. It is unknown how the binding of AβOs to predominantly dendritic synaptic sites leads to FAT impairment. Because CaN, its effectors, and motor proteins associated with DCVs are present in both dendrites and axons, we investigated whether AβOs induce dendritic, CaN-dependent transport defects that precede FAT disruption. We assessed dendritic DCV transport by live cell imaging of cultured mouse hippocampal neurons using fluorescently-tagged brain-derived neurotrophic factor (BDNF-mRFP) and

neuropeptide Y (NPY-mCherry). AβOs induced dendritic and axonal DCV transport defects simultaneously; however, severe dendritic transport defects were observed 8-12 h prior to maximal impairment of FAT. These defects were reversed by inhibition of CaN with FK506. We next examined whether the spatiotemporal progression of transport defects correlates with changes in resting cytosolic calcium. FRET-based cameleon imaging revealed that calcium elevation in dendrites and axons coincided with DCV transport disruption. Our findings suggest that AβO-induced dendritic transport defects precede FAT disruption through dysregulated calcium signaling during early AD pathogenesis.

1-C-63 Pain and Cellular Activation in Experimental Autoimmune Encephalomyelitis (EAE)

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Central neuropathic pain is a highly prevalent and poorly understood symptom of multiple sclerosis (MS). In MS, widespread inflammation in the central nervous system (CNS), alongside demyelination and neurodegeneration provokes errant sensory signaling through undetermined mechanisms. The disease model experimental autoimmune encephalomyelitis (EAE) shares many underlying pathological characteristics with MS, and can be used to study pain in the disease. Mice with EAE develop robust allodynia and pain hypersensitivity prior to the onset of paralysis. We have now conducted in vivo optical (flavoprotein autofluorescence, FA) imaging and show that responses to tactile stimulation in the primary somatosensory cortex (S1) are exaggerated in EAE, a finding that implicates cortical plastic mechanisms in the pathogenesis of neuropathic pain in EAE. Using these methods, we are assessing novel treatments for pain in EAE such as the monoamine-oxidase inhibitor phenelzine (PLZ). Preliminary results demonstrate that PLZ not only reduces the severity of the disease, but also diminishes neuropathic pain behaviors compared to vehicle-treated mice at matched disease severity. A better understanding of how PLZ and other drugs act to diminish pain in EAE may lead to new therapeutics for neuropathic pain in MS.

1-C-64 Distribution and function research of DBP in CNS

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Objective To examine expression and significance of vitamin D-binding protein (DBP) in the cerebral cortex and spinal cord of rats, as well as the primary cultured neurons isolated from rats. Methods DBP expression in the cerebral cortex and spinal cord of Wistar rats was detected by immunohistochemistry. The primary neurons culture was undergone using cerebral cortex and spinal cord isolated from rat fetuses. Then the expression of DBP mRNA of tissues and neurons was examined by reverse transcription. Results There was the distribution of DBP and its mRNA in the cytoplasm of neurons of rat spinal cord; however, DBP and its mRNA did not exist in the cerebral cortex and neurons. Conclusions This study discovered that neurons in the rat spinal cord could synthesize DBP but not neurons cultured in vitro, which indicated that the expression of DBP gene required specific environment. This study is beneficial for further investigating the function of DBP in the central nervous system diseases.

1-C-65 Nlrx1 regulates neuronal survival

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The regulation of neuronal survival is an essential process that maintains central nervous system (CNS) homeostasis during healthy state and disease. Multiples intracellular pathways contribute to the survival of neurons during adverse conditions such as increased inflammation and hypoxia. Recently discovered family of proteins, nucleotide-binding domain leucine-rich repeat-containing proteins (NLRs) act as molecular switches that

redirect multiple signalling pathways. Although, mainly studied in context of immune system, Nlrs regulate fundamental processes of cell survival, proliferation, and death that are important in all cell types. We studied the role of one of the NLR proteins, NLRX1, in neuronal survival in a context of increased cytokine concentration and hypoxia. Previous research demonstrated that Nlrx1 regulates immune responses during viral infection. We found that HuSH-29 RNA driven knockdown of the Nlx1 expression from N2A cell severely compromised their survival. Using flow cytometry, we observed increased degree of apoptosis in the Nlrx1 deficient cells compare to the cells transfected with scrambled HuSH control. In addition, we found that the deletion of NLRX1 lead to the decrease expression of Beclin 1 suggesting altered kinetics of autophagy in the Nlrx1 deficient cells. Results of this study suggest potential mechanisms to target during neuroinflammatory diseases such as stroke or trauma.

1-C-66 Neurprotective effects of oleuropein in a 6-hydroxydopamine (6-OHDA) model of Parkinson's disease

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Oleuropein (Ole), a phenolic compound found in the olive leaf from Olea europaea, is known to possess several pharmacological benefits, including antioxidant and anticarcinogenic properties. The aim of this study was to investigate whether Ole may protect neuronal cells against oxidative stress and apoptosis in a cellular model of Parkinson's disease (PD), neuronal PC12 cells exposed to the potent neurotoxin 6-hydroxydopamine (6-OHDA). Cytotoxicity assays showed that the administration of Ole prior to the oxidative insult prevents cell death induced by 6-OHDA. Furthermore, the results obtained by measuring the expression of several pro- and anti-apoptotic proteins, such as Bax, Bcl-2 and PARP 1, and by DNA fragmentation, demonstrate that Ole significantly decreases apoptosis. Since a growing body of evidence shows that autophagy plays an important role in the pathogenesis of PD, we also observed autophagic vacuoles in the cytoplasm of neuronal cells treated with Ole and we identified them by labeling with acridine orange, Cyto-ID and by measuring LC3 expression. Altogether, these results suggest that Ole has interesting neuroprotective properties which might be related to the increased number of autophagic vacuoles. Other studies are in progress to better define the role of Ole in apoptosis and autophagy.

1-C-67 Examining the validity of the MK-801 pre-clinical animal model of schizophrenia: Assessing brain metabolic activity via PET and CT fused imaging in live rats

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Chronic administration of N-methyl-D-aspartate (NMDA) receptor antagonists has been shown to lead to schizophrenia-like abnormalities in humans as well as in animals, providing support for a glutamatergic dysfunction in schizophrenia. One such antagonist is dizocilpine maleate (MK-801), which non-competitively blocks the NMDA receptor complex. The objective of this study was to examine the validity of the MK-801 pre-clinical model of schizophrenia across several established behavioural analyses and through an innovative evaluation of brain metabolic function Male Sprague-Dawley rats were treated acutely or sub-chronically with MK-801 and tested for abnormalities in sensorimotor gating, locomotor activity, performance in the 8-arm radial maze and social interaction. Brain metabolic activity was measured with positron emission tomography (PET) and computerized tomography (CT) fused imaging of 18-Fluorodeoxyglucose ([18F]FDG) uptake in the brain. Rats treated acutely with MK-801 at 0.5 mg/kg exhibited deficits in pre-pulse inhibition, social withdrawal, disrupted performance in the 8-arm radial maze, hyperlocomotor activity, and increased [18F]FDG uptake in the prefrontal cortex The acute MK-801 animal model provides a viable

pre-clinical basis to study schizophrenia-like abnormalities. Furthermore, these results demonstrate that brain metabolic function assessed with PET and CT fused imaging in live rats is a robust analysis to assess the content and face validity of animal models of schizophrenia and subsequently to investigate novel therapies for this disorder.

1-C-68 Synapsin II knockdown in medial prefrontal cortex causes hypofrontality and neurobiological alterations comparable to schizophrenia

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"Hypofrontality", or decreased glucose utilization in the frontal cortex has been characterized in subjects with schizophrenia. Evidence also suggests a dysregulation of several neurotransmitter systems in SZ. The dopamine and glutamate hypotheses attribute hyperdopaminergic activity in the subcortical regions and hypoglutamatergic activity in the cortical regions of the brain, respectively. Glutamate hypoactivity occurs on GABA interneurons, and can dysregulate GABAergic neurotransmission. Synapsins are neuron-specific phosphoproteins which bind and regulate synaptic vesicles. Synapsin (syn) II has also been shown to be a candidate gene for SZ. Thus, subnormal expression can cause imbalances in local and long-loop circuitry by altering neurotransmitter concentrations and associated vesicular neurotransmitter transporter levels, contributing to the development of SZ. The objective of this study was to investigate whether syn II knockdown in the medial PFC results in hypofrontality, and correlates with changes in vesicular transporter levels. Knockdown of syn II caused SZ-like behavioural abnormalities (increases in locomotor activity, decreases in PPI, decreases in social interaction) and cortical hypofrontality. Further, immunoblotting showed biochemical alterations comparable to that of SZ, including decreases in glutamate and GABA transporter levels. Results will provide clues into the etiology of the disease, and lend to the development of effective treatment and prevention strategies targeting SZ.

1-C-69 Modelling Autism Spectrum Disorder Through Maternal Immune Activation In Mice

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social interaction and communication as well as ritualistic repetitive behaviours. Apart from genetic predisposition, epidemiological studies suggest that maternal immune activation (MIA) during pregnancy may also be a risk factor for ASD. This theory is supported by the presence of activated astrocytes and microglia in human post-mortem brain samples and changes in cytokine levels in the sera of ASD patients. To study MIA in a laboratory setting, we injected mouse dams (C57BL/6) with lipopolysaccharide (LPS) or polyinosinic:polycytidylic acid (Poly I:C) during mid-gestation to mimic a bacterial or viral infection, respectively. The offspring produced (i.e. LPS 1X or Poly IC 1X) were compared with offspring from dams that were injected during two consecutive pregnancies (i.e. LPS 2X or Poly IC 2X). Once the offspring reached adulthood, male and female mice were analyzed separately and compared with saline controls. We investigated ASD-associated behaviours including motor activity, social interaction and repetitive behaviour using the automated activity box, modified three-chamber paradigm, and marble burying test, respectively. Pathological analyses were subsequently conducted on the cerebellum by measuring the expression of microglia, astrocyte, and mature oligodendrocyte markers using immunohistochemistry/western blot. The results indicate the presence of several ASD-like behaviours and pathologies in the MIA offspring, some of which are sex-dependent.

1-C-70 Striatal dopamine depletion and cortical dopamine receptor changes in Parkinson's disease with mild cognitive impairment

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Mild cognitive impairment in Parkinson's disease (PD-MCI) is common and is a risk factor for dementia. There is evidence for both nigrostriatal and mesocortical dopamine (DA) dysfunction in PD, however the pathology of PD-MCI is unknown. The objective was to investigate striatal dopamine depletion and cortical dopamine receptor changes in PD-MCI using Positron Emission Tomography (PET). We recruited PD-MCI(n=8), cognitively normal PD patients(PD-CN)(n=12), and aged-matched healthy controls(HC)(n=13). PD-MCI was diagnosed according to MDS task force criteria: At least 1.5 standard deviations below the normative mean on two tests of a neuropsychological battery. Subjects were scanned with [11C] DTBZ to examine stratal DA depletion, and with [11C] FLB 457 to measure cortical D2 availability. Binding potential was the outcome measure. [11C] DTBZ BP was significantly reduced in PD-MCI compared to HC and PD-CN in the associative striatum. D2 availability was significantly reduced in PD-MCI compared to HC bilaterally in the insula and inferior temporal lobe, and the right parahippocampal gyrus. PD-MCI had reduced binding compared to PD-CN in the bilateral insula and right parahippocampal gyrus. There was a positive correlation between global cognitive function and D2 availability in the right insula, and between semantic fluency and D2 availability in the left parahippocampal gyrus. This study demonstrated both nigrostriatal and cortical DA dysfunction related to cognitive impairment, providing the first evidence of cortical DA receptor changes that parallel striatal changes.

1-C-71 Regulation of tau exon 10 splicing during mouse brain development

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Tau is a microtubule (MT)-associated protein abundant in the axons of neurons. Its main known function, to bind and stabilize MT, is mediated by a MT binding domain consisting of 3 or 4 repeat regions. The alternative splicing of tau exon 10 results in the presence or the absence of a MT-binding repeat, leading to the expression of tau with either four (4R-tau) or three MT-binding repeats (3R-tau). During development, 3R-tau is expressed from the embryonic stages but 4R-tau expression begins after birth. Approximately, an equal amount of 3R-tau and 4R-tau is expressed in normal adult human brain. An alteration of this ratio is thought to be causing several neurodegenerative tauopathies. Alternative splicing is regulated by splicing factors such as Serine/arginine-rich (SR) proteins and kinases, which phosphorylate SR proteins and regulate their function. There is some evidence that SR proteins trigger either the inclusion or the exclusion of tau exon 10. The purpose of this study is to analyze the regulation of the exon 10 splicing and develop a better understanding of the mechanisms involved in the differential expression of 3R-tau and 4R-tau throughout development. We have analyzed the expression of tau, of the SR proteins involved in exon 10 splicing, and of the kinases known to phosphorylate these splicing factors. Overall, our results show an increase of SR proteins promoting the inclusion of exon 10 and, conversely, a decrease of those promoting exclusion during post-embryonic development, which is consistent with the profile of expression of tau isoforms.

1-C-72 Hippocampal excitability is increased in aged mice

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Aging is known to be associated with a high risk of developing seizure disorders. Currently, the mechanisms underlying this increased seizure susceptibility are not fully understood. Several previous studies have shown a loss of subgroups of GABAergic inhibitory interneurons in the hippocampus of aged rodents, yet the network excitability intrinsic to the aged hippocampus remains to be elucidated. The aim of this study is to examine age-dependent changes of hippocampal network activities in young adult (3-5 months), aging (16-18 months), and aged (24-28 months) mice. We conducted intracranial electroencephalographic (EEG) recordings in free-moving animals and extracellular recordings in hippocampal slices in vitro. EEG recordings revealed frequent spikes in aging and aged mice but only occasionally in young adults. These EEG spikes were suppressed following diazepam administration. Spontaneous field potentials with large amplitudes were frequently observed in hippocampal slices of aged mice but rarely in slices from young adults. These spontaneous field potentials originated from the CA3 area and their generation was dependent upon the excitatory glutamatergic activity. We therefore postulate that hippocampal network excitability is increased in aged mice and that such hyperactivity may be relevant to the increased seizure susceptibility observed in aged subjects.

1-C-73 Differential Effects of Neurosteroids and Anticonvulsant Drugs on Drug-Refractory Seizures and Spontaneous Epileptiform Discharges in the Mouse

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Electrical kindling is a model of drug-refractory seizures and measures anticonvulsant efficacy. Inter ictal discharges (IIDs) are epileptiform activities that reflect overall excitability of the brain. While the anticonvulsive drug therapy is the most widely employed approach to seizure control in clinical practice, the concept of using intrinsic anticonvulsive mechanisms, such as neurosteroid-mediated inhibition, remains an attractive therapeutic option. Using a novel mouse model of hippocampal electrical kindling, we investigated the anticonvulsant efficacy of pregnanes and anticonvulsant drugs against partial and generalized seizures. We also examined the effects of some of these treatments on spontaneous IIDs in fully kindled mice. The compounds tested were progesterone and its metabolites, 5α-dihydroprogesterone (DHP) and 5α,3α-tetrahydroprogesterone (THP, also called allopregnanolone). The anticonvulsant drugs carbemazepine, fosphenytoin, and midazolam were also tested. Progesterone, THP, carbamazepine and midazolam significantly reduced behavioral seizures. The seizure stage reduction by progesterone, THP or midazolam was associated with diminished EEG afterdischarges. THP suppressed IIDs, and both focal and generalized seizure activities, but progesterone is only effective against generalized seizures. We suggest that GABAergic anticonvulsant drugs mimic the actions of THP on anticonvulsant and IID frequency, but progesterone does not. Given these results, progesterone and THP may exert anticonvulsant actions, at least partly, through different mechanisms.

1-C-74 Potassium Channel Deficiency Enhances Cerebellar Inhibitory Transmission in Fragile X Syndrome

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New roles for the cerebellum in higher-order functions such as cognition, language and social function make it an attractive area of study for neurodevelopmental diseases such as Autism Spectrum Disorder and Fragile X Syndrome (FXS). In this study we examined cerebellar inhibitory transmission in the FMR1 KO mouse, a model of FXS. Patch clamp recordings revealed a robust reduction in the firing rate of Purkinje cells (PC) and

an increase in spontaneous inhibitory postsynaptic currents, indicating enhanced synaptic inhibitory input in KO mice. Inhibitory inputs from GABAergic basket cells can regulate PCs so we examined the expression of presynaptic proteins in these cells. In KO mice, expression of the presynaptic potassium channel Kv1.2 was reduced in the pinceau, the specialized structure that forms the axon terminal of basket cells. Immunoprecipitation experiments revealed that Kv1.2 mRNA binds to FMRP, the mRNA binding protein that is absent in FXS, suggesting a possible mechanism for Kv1.2 downregulation in the KO. These findings suggest increased spontaneous GABA release by basket cells onto the PC, explaining the reduced firing rate observed in KO PCs. The expression of the synthetic enzymes GAD65 and GAD67 was also reduced in the pinceau of adult KO mice, possibly as a compensatory response to elevated GABA release. This is the first report of reduced PC firing rate in FXS resulting from excessive basket cell GABA release due to underexpression of Kv1.2. These findings implicate excessive cerebellar inhibitory tone as an important mechanism in the pathology of FXS.

1-C-75 Trytophan hydroxylase levels in brainstem serotonergic neurons after withdrawal from an enriched environment with exercise

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We have previously reported that environmental enrichment (EE) with exercise significantly reduces the number of tryoptophan-hydroxylase (TPH)-positive cells in the brainstem dorsal raphe. In the present experiment we studied whether these changes persist after withdrawal from EE. Three cohorts of male Sprague-Dawley rats were studied: 1) The SE animals were singly housed for 10 weeks in a standard cage with no access to enrichment; 2) The EE cohort was group housed for 10 weeks in an enriched environment, which included free access to running wheels and various enrichment objects that were changed and rearranged three times a week; 3) The EEW cohort was housed in the enriched environment for 10 weeks then transferred to standard un-enriched housing, one per cage, for an additional three weeks. Sections of dorsal raphe were processed for TPH immunohistochemistry. The number of TPH-positive cells was determined by blinded, manual counting. Results were analyzed by analysis of variance (ANOVA) followed by post-hoc Tukey and t-tests, where appropriate. The cohort of animals housed in an enriched environment (EE) showed a significant 25% reduction in TPH-immunoreactive cells in the DRN compared with SE controls. By contrast, the EEW cohort, which had been housed in the enriched environment for 10 weeks then transferred to the other environment, showed no difference compared with controls. TPH-immunoreactivity was significantly lower (17%) in the EE group than in the EEW cohort. These results show that the effects of EE on serotonergic neurons are transient.

1-C-76 Mechanism of tau hyperphosphorylation in Type-2 diabetic mice

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Background: Hyperphosphorylated tau is the major component of paired helical filaments in neurofibrillary tangles found in Alzheimer's disease (AD) brains, and tau hyperphosphorylation is thought to be a critical event in the pathogenesis of the disease since it correlates with the degree of cognitive impairment in AD. Only a small proportion of AD is due to genetic variants, the large majority of cases is late onset and sporadic in origin. The cause of sporadic AD is likely to be multifactorial, with external factors interacting with biological or genetic susceptibilities to accelerate the manifestation of the disease. Diabetes mellitus (DM) might be such factor, as there is a lot of data from epidemiological studies suggesting that DM is linked with an increased relative risk for AD.

However, the consequences of DM on AD pathology are not well understood. Thus, we studied the impact of type 2 diabetes (T2DM) on tau pathology in mice. Methods: We investigated tau phosphorylation and its mechanisms in db/db mice, a well-established mouse model of T2DM. Results: We observed tau hyperphosphorylation in the brain of db/db mice, and we show that this hyperphosphorylation is probably due to a deregulation of specific kinases/phosphatases activities. Conclusions: This study reports that diabetes induces AD-like tau hyperphosphorylation in the mouse brain, with patterns resembling those in early AD brains. This research will help understanding the link between DM and AD, for the development of future treatments or life style strategies destined to check the advance of the disease.

1-C-77 Frontal Lobe EEG activity and Saccadic Eye Movement Tasks in the Assessment of Cognitive Deficits in Fetal Alcohol Spectrum Disorder (FASD)

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Recently developed brain-computer interface devices record electroencephalogram (EEG) activity using a single dry-sensor electrode and provide data comparable to that obtained from multi-channel EEG systems. Our lab has previously shown that saccadic eye movement tasks probe executive functions (e.g., spatial working memory) and are a sensitive measure of cognitive dysfunction in children with a Fetal Alcohol Spectrum Disorder (FASD). We sought to quantify the relationship between frontal lobe EEG activity in children and performance on eye movement tasks with varying cognitive loads, and to determine whether frontal lobe EEG activity in children with an FASD correlates to performance deficits. Children with or without an FASD diagnosis performed a memory-guided eye movement task and EEG was recorded using the Neurosky Mindwave©. Factor analysis revealed that the FASD group made errors in remembering the spatial location of a visual stimulus more frequently than the control group. In the control group, alpha band activity in the frontal lobes was correlated with correct trials. During trials in which errors were made, the FASD group exhibited greater relative theta band activity. The results suggest that single-channel EEG recording can be used to identify neural mechanisms underlying deficits in saccadic eye movement task performance in children with an FASD. Additionally, portable single-channel devices offer greater user comfort than typical EEG recording equipment and flexibility for use outside the laboratory, which will facilitate the study of children with an FASD.

1-C-78 Single neuron properties promote onset of the persistent vegetative state

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Thousands of patients lie in a Persistent Vegetative State because their brainstem has survived a period of cardiac arrest that destroys regions of higher brain (cortex/striatum/thalamus). Here we show that neurons of hypothalamus/brainstem easily survive a period of oxygen-glucose deprivation (OGD) that invariably kills higher neurons. Coronal slices from adult rat underwent 10 min OGD during whole cell recordings in neocortex (n=20), CA1 (n=9), striatum (n=10), thalamus (n=12), hypothalamus (PVN n=20; SCN n=18), midbrain-pons (Mes.N n=14; LC n=8) and medulla (Sol.N n=31; DMV n=12). Anoxic depolarization (AD) in higher neurons was always 'terminal' i.e., a fast onset to zero mV without recovery of membrane potential (Vm) or cell input resistance (Rin) post-OGD. In contrast, depolarization in hypothalamus/brainstem was 'resistant': i.e., a slow AD to -20 mV with rapid recovery of Vm and Rin post-OGD. The thalamus-hypothalamus interface divided terminal vs resistant responses. Without a robust AD, recovery by lower neurons was remarkably swift and survived multiple bouts of OGD. The Na/K ATPase pump inhibitor ouabain (100 uM) mimicked OGD-induced AD in each neuronal type, including only a minor depolarization by neurons in mesencephalic

nucleus where the pump clearly keeps working. Thus lower neurons can resist and recover from ischemic periods that shut down and then kill higher neurons. This clear regional difference in neuronal properties promotes vital functions (breathing, cardiac control) but with the higher neuron loss typical of the Persistent Vegetative State.

1-C-79 Chronic deep brain stimulation of the ventral medial frontal cortex produces lasting firing rate increases in dorsal and median raphe nuclei

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Long-term, high-frequency stimulation (i.e., deep brain stimulation, or DBS) of the ventral medial prefrontal cortex increases the amount of effort an animal will exert in an inescapable environment, such as in the forced swim test (Hamani et al., 2009). This effect disappears following damage to the serotonergic system, suggesting that DBS may influence behavior by acting on serotonin-containing projection neurons in the raphe nuclei. The present study investigated the effects of DBS by electrophysiologically recording from the dorsal and median raphe nuclei of urethane-anesthetized rats previously treated with nine days of either DBS or sham stimulation. More than half of all neurons were found to fire at preferred phases of the prefrontal delta (0.5 to 2 Hz) oscillation (alpha = 0.01); while raphe neurons fired at positive phases, cells recorded from regions outside of the raphe nuclei fired most at negative delta phases. Median firing rates of raphe neurons were higher in DBS-treated rats compared with controls (p = 0.01). In contrast, no effect of DBS was observed on neurons recorded outside of the raphe nuclei (p = 1.0). Changes did not appear to be specific for wide-waveform neurons (putative projection neurons) or narrow-waveform neurons (putative interneurons), nor for neurons recorded from the dorsal compared with median raphe nucleus. The results suggest that DBS induces lasting changes in either the strength of innervation or intrinsic excitability of raphe neurons, consistent with a role of the serotonergic system in the effects of DBS on motivation.

1-C-80 Iron homeostasis and mitochondrial dysfunction in Relapsing-remitting and Chronic Experimental autoimmune encephalomyelitis (EAE)

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The mechanism underlying iron accumulation in the brain in MS is not known. We used EAE to study iron homeostasis in the spinal cord in relapsing-remitting (RR) and chronic (CH) forms of EAE. Mice were sacrificed at the onset, peak and remission stages of EAE as well as 8-9 weeks after induction ('end stage'). Iron levels measured with the ferrozine assay were significantly higher in both models of EAE at all stages and this was confirmed by ferritin immunoreactivity. The mRNA expression of molecules involved in iron homeostasis was assessed. The heavy chain of ferritin, ferritin light chain, ceruloplasmin, hephaestin, and DMT1 increased at onset and/or peak stages in both models of EAE. Finally, a PCR-array for mitochondrial oxidative stress related genes showed an overall downregulation (>2 fold) in the RR and CH EAE group at peak stage for most of the complex I, II, III, IV and V genes compared to naïve controls. In the CH EAE at 'end stage' there was only an upregulation of a few genes from complex IV and V. To test if iron plays a role in the development of EAE, mice with RR-EAE were treated either with the iron chelator SIH (salicylaldehyde isonicotinoyl hydrazone) 50mg/kg or vehicle. The group treated with SIH had a lower score at the onset and peak as compared to the vehicle treated group. These results suggest that iron plays an important role in the development of EAE, and that there is dysfunction of genes related to mitochondrial oxidative stress that could be associated with increased iron levels.

1-C-81 Macrophage polarization in vitro and in vivo after spinal cord injury

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Macrophages/microglia are activated after CNS injury and have both detrimental and beneficial effects. Recent work suggests that the tissue environment influences macrophage polarization towards different phenotypes, referred to as M1 and M2. M1 polarization includes the production of nitric oxide and pro-inflammatory cytokines, while M2 macrophages are anti-inflammatory and help in wound healing and tissue repair. A previous study reported that M1 markers dominate the macrophage response after spinal cord injury (SCI). Myelin phagocytosis in vitro by macrophages was also shown to reduce secretion of pro-inflammatory cytokines. We therefore characterized the effects of myelin phagocytosis on the expression of various cell surface and intracellular M1 and M2 makers in vitro using fluorescence activated cell sorting (FACS). Our results indicate that myelin phagocytosis by M1 polarized bone marrow derived macrophages (BMDM) and microglia induces a shift in polarization from an M1 to an M2 state. Since significant myelin phagocytosis occurs in the first 2 weeks after SCI, we examined macrophage polarization in vivo after SCI using multi color FACS to identify expression of M1 and M2 markers at various times after spinal cord contusion injury. Our results indicate that macrophage/microglia express a predominantly M1 phenotype despite their phagocytic activity. We assessed factors in the environment that may influence such M1 polarization. Our in vitro and in vivo studies suggest that TNF-α induces changes in the injured CNS environment that favors M1 polarization.

1-C-82 Deficits in response inhibition correlate with measures of oculomotor control in children with Fetal Alcohol Spectrum Disorder (FASD) and Prenatal Alcohol Exposure (PAE)

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Children with FASD or PAE frequently exhibit impairment on tasks measuring inhibition. Saccades are rapid eye movements that bring new visual targets onto the fovea of the retina, and measurement of eye movement control is a powerful tool for assessing sensory, motor and cognitive function. The objective of this study was to determine if a performance-based relationship exists between psychometric tests and eye tracking tasks in children with FASD. Participants for this dataset were aged 5-18 years and included those diagnosed with an FASD (n=72), those with PAE but no clinical FASD diagnosis (n=21), and typically developing controls (n=139). Participants were tested on a neurobehavioral test battery, consisting of subtests from the NEPSY-II, which measure attention and inhibition. Participant also completed a series of saccadic eye movement tasks, consisting of the antisaccade and memory-guided tasks, which measure response inhibition and working memory. On the psychometric test battery, both the FASD and the PAE groups performed worse than controls on measures of attention and inhibition. Compared with controls, the FASD group made more errors on both the antisaccade and memory-guided saccade tasks. Among the FASD/PAE group, inhibition and switching errors were highly correlated with direction errors on the antisaccade task but not on the memory-guided task, and there were no significant correlations in the control group. This data suggests that response inhibition deficits in children with FASD/PAE are associated with difficulty controlling saccadic eye movements.

1-C-83 Endogenous tau regulation in a miRNA knockout mouse model

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BACKGROUND: It is well established that changes in the regulation of tau expression and/or splicing are involved in the development of tauopathies, a group of neurodegenerative disorders including Alzheimer's disease (AD). Recently, we have shown that microRNAs, and in particular miR-132, participate in the regulation of tau expression and splicing in neuronal cells in culture. Interestingly, miR-132 is among the most strongly down-regulated miRNAs in tauopathic brain in humans. Our goal now is to follow-up on these observations by investigating the role of miR-132 in the regulation of tau metabolism in vivo METHODS: We used miR-132 knockout (KO) mice as biological models. Mice were sacrificed at various ages in order to study tau. This was done by western blot, PCR, and real-time quantitative RT-PCR RESULTS: We demonstrate that endogenous tau splicing, expression, and phosphorylation are affected by the absence of miR-132 in vivo. Interestingly, the effects on tau metabolism seem age dependent CONCLUSION: Our results validate previous findings in cells and support the hypothesis that miR-132 function is critically involved in the regulation of tau metabolism in the brain. Further experiments are underway to understand the relationship between miR-132 loss, abnormal tau modulation, and neurodegeneration.

1-C-84 Neuroprotective effects of the phytosterol Cucurbitacin E via the autophagic pathway in a cellular model of Parkinson's disease

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Currently, natural molecules are under intensive analysis for their potential as preventive and/or adjuvant therapies for neurodegenerative disorders, such as Parkinson's disease (PD). We evaluated the neuroprotective potential of Cucurbitacin E (CuE), a phytosterol extracted from the Cucurbitaceae Ecballium elaterium, using a cellular model of PD. In our experimental paradigm, PC12 cells are differentiated as dopaminergic neurons by exposure to nerve growth factor (NGF). They are then treated with the potent parkinsonian toxin MPP+ to provoke an important oxidative stress and enhance apoptosis. CuE is administered prior and during the neurotoxic treatment. We then measured cytotoxicity, apoptosis and reactive oxygen species to evaluate cellular oxidative stress and the antioxidant properties of CuE. Cellular macroautophagy, a bulk degradation process involving the lysosomal pathway, was also analyzed by fluorescence microscopy. Neuroprotective CuE effects at the cellular level were observed by a reduction in both MPP+ - induced cell death and apoptosis, from 20.1% to 3.6% and from 125% to 109% respectively. While microscopy analyses did show an enhancement of the autophagic flux in the presence of CuE, antioxidant assays failed to demonstrate the ability of CuE to rescue neuronal cells from oxidative stress. Together these data show that oxidized proteins and organelles are degraded by macroautophagy and suggest a likely mechanism by which CuE exerts neuroprotective effects in the context of PD-associated neuronal death.

1-C-85 Potential role of PTEN nuclear translocation in excitotoxic neuronal death in Huntington's Disease

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Huntington Disease (HD) is a disorder resulting from degeneration of striatal medium spiny neurons.Several lines of evidence indicate that excitotoxicity as a result of N-methyl-D-aspartate receptor (NMDAR) over-activation has a role in neuron death observed in HD. Yet, mechanisms are poorly characterized. Recent studies in our lab demonstrate that excitotoxic NMDA stimulation causes nuclear translocation of the tumor suppressor PTEN (Phosphatase and Tensin homolog

deleted on chromosome ten) via mono-ubiquitination of PTEN at lysine13 (K13) and that blocking PTEN nuclear translocation using a membrane permeable interference peptide flanking K13 (TAT-K13) developed by our lab significantly reduces NMDAR-mediated excitotoxic neuronal death.These results lead us to our study aimed at investigating a potential role of PTEN nuclear translocation in excitotoxic neuronal death in HD using YAC128 HD transgenic mice.We found a significant increase in PTEN nuclear translocation after excitotoxic NMDA stimulation in cultured primary hippocampal and striatal neurons from HD mice.Translocation could be largely inhibited by bath application of TAT-K13.Consistent with the causal role of PTEN nuclear translocation in excitotoxic neuronal death, we demonstrated that blocking PTEN nuclear translocation using TAT-K13 significantly reduced NMDAR-mediated excitotoxic death in HD transgenic neurons.Our results suggest that PTEN nuclear translocation may have a role in NMDAR-mediated excitotoxic neuronal death in HD and may represent a new target upon which novel therapies for HD can be developed

1-C-86 Mathematical models explain altered brain activities in a mouse model of Rett syndrome

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Rett syndrome (RTT) is a developmental disorder caused by mutations in the gene MECP2 located on the X chromosome. Despite having a clear genetic origin of this disorder, cellular and network mechanisms for RTT remain elusive. Can we make sense out of this complex genetic-network-behavioural relation? Zhang et al. (2008) have previously shown altered characteristics of an inhibition-based slow population activity (SPA) in hippocampal slices of a RTT mouse model. When compared to wild-type, RTT hippocampal SPAs have lower frequencies but higher amplitudes. In addition, RTT preparations are more excitable, eliciting excitatory sharp wave-like activities more easily. We use mathematical modeling, simulations and analyses to help illuminate the underlying basis for these changes. Using model networks of fast-spiking inhibitory cells, we have earlier shown that SPAs can arise via a network multi-stability mechanism that is critically dependent on excitatory fluctuations. Here, we show that the observed changes in SPA characteristics in RTT can arise due to a decrease in excitatory fluctuations in our models. Our simulations further show that this decrease in excitatory fluctuations can lead to increased propensity for excitatory networks to exhibit sharp wave-like behaviour. Our work thus identifies a critical connection between excitatory fluctuations and altered network activities in a RTT model. These results suggest that therapeutic interventions targeting fluctuation ('noise') manipulations may be more beneficial.

1-C-87 The effect of an anti-amyloid beta peptide aggregation compound on adult hippocampal neurogenesis in an Alzheimer's disease mouse model

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The naturally occurring inositol stereoisomer, scyllo-inositol, is an anti-amyloid beta peptide (Aß) aggregation compound. Previous studies have shown that administration of scyllo-inositol to the TgCRND8 model of Alzheimer's disease reduces Aß pathology and improves cognitive function. However, the mechanism responsible for improved cognition has not been fully elucidated. The study aim is to assess the effect of scyllo-inositol treatment on adult hippocampal neurogenesis. To assess this TgCRND8 and wildtype mice were injected once/day with bromodeoxyuridine (BrdU) for 5 days to label proliferating cells. The phenotype of proliferating cells was assessed through immunofluorescence staining for BrdU, doublecortin (early neuron marker) and glial fibrillary acidic protein (GFAP; astrocyte marker). To assess the effect of scyllo-inositol treatment on

hippocampal cell survival, the BrdU protocol was repeated, except the mice were sacrificed 21 days after the last injection. The surviving cell phenotype was assessed by staining for BrdU, neuronal nuclei (mature neuron marker) and GFAP. scyllo-Inositol treatment of TgCRND8 mice significantly increased the percent of newborn cells that were doublecortin positive, such that the percent was not different from wildtype mice. scyllo-Inositol treatment also significantly increased the number of newborn cells that survived the 21 day incubation period and increased the percent of these cells expressing the mature neuron marker. These findings provide an additional mechanism for improved cognition in scyllo-inositol treated TgCRND8 mice.

1-C-88 Age-related changes in inflammation after intracerebral hemorrhage

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Stroke is the third leading cause of mortality and morbidity in the developed world. Intracerebral hemorrhage (ICH) is a devastating form of stroke; mortality is ~50% by 6 months and ~80% of survivors fail to regain functional independence. In the hours to days after both forms of stroke, an inflammatory response ensues, with activation of resident microglia and astrocytes, infiltration of circulating immune cells, and up-regulation of numerous genes. In experimental models of ischemic stroke and ICH, we and others have analyzed expression of mediators that can exacerbate blood-brain barrier disruption or can be directly neurotoxic (e.g., MMPs, pro-inflammatory cytokines, nitric oxide), and anti-inflammatory mediators and growth factors that potentially aid long-term repair and recovery. Evidence is accumulating that expression of specific mediators depends on time and location after the injury, likely reflecting the microenvironment around the lesion. Although stroke is mainly a disease of aging, most experimental studies have used young animals; thus, our goal is to better delineate how aging affects the evolution of inflammation after stroke. Here, we used real-time RT-PCR to compare expression of several genes (including, IL-1á, IL-4, IL-6, IL-10, IL-13, TNFá, TGFâ) in the striatum of aged and young adult rats over the first 7 days after ICH (induced by injecting collagenase). In aged rats, the overall inflammatory response was less pronounced, often delayed, and the balance between pro- and anti-inflammatory mediators was altered.

1-C-89 Brain-derived neurotrophic factor and TrkB expression in the ""oldest-old"", the 90+Study: correlation with cognitive status and levels of soluble amyloid-beta

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An increasing population of nonagenarians and centenarians suffer from various forms of dementia, mainly Alzheimer's disease (AD). Brain-derived neurotrophic factor (BDNF) is vital for learning and memory and is decreased in the AD brain; this reduction correlates with the degree of cognitive deficit. Recent studies suggest soluble amyloid-β (Aβ42) as the toxic species in AD, rather than insoluble plaques. It is unknown whether AD-type neuropathology, soluble Aβ42 or levels of BDNF and its receptor TrkB correlate with cognitive status in the oldest old Here we examined BDNF and TrkB mRNA expression and levels of soluble Aβ42 and their association with cognitive status and AD pathology of subjects over 90 years old. Subjects were demented or with normal cognition, and with Aβ and tau pathology or pathology-free. A significant decrease in BDNF expression was observed in the demented group with AD pathology compared to controls without dementia or pathology, and the demented group without AD pathology exhibited a strong trend toward lower BDNF. BDNF mRNA expression correlated with MMSE scores of the subjects. There was no difference between groups in expression of TrkB isoforms. Significant increases in the amount of

soluble Aβ42 were found between both groups with AD pathology, demented or not, and the non-demented no-pathology control group. MMSE scores were negatively correlated with soluble Aβ42 and with Braak and CERAD scores. Thus, soluble Aβ42 levels and BDNF expression, but not TrkB expression, correlate with the degree of dementia in the oldest old.

1-C-90 Distribution of retrogradely labelled neurons in partial cortical deafferentation model of epileptogenesis

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Traumatic brain injury, one of the causes of epilepsy, can be followed by certain electrophysiological and cytoarchitectonic changes. We found previously that local connection probability increases after neocortical deafferentation in the model of injury-induced epileptogenesis, which suggests that remodelling of cortical connections can occur as a result of head trauma. Morphological data, however, are insufficient to support this hypothesis. In this study we investigated neocortical connectivity using retrograde tracing. Four cats underwent transsection of the white matter in the suprasylvian gyrus (undercut, UC) and 50-69 days after the surgery cholera toxin subunit B, at a volume of 100 nl, was injected both in the deafferented and the contralateral gyrus, followed by 40-h survival time. CTB-stained cells were marked in Neurolucida. We have found different distribution of CTB-stained neurons in the deafferented verus contralateral hemisphere. The injured gyrus was characterised with clear asymmetry of stained neuron distribution, with more extensive staining in the rostral part of the cortex, while cell distribution in intact hemisphere was near Gaussian, with the highest values at the centre of injection site. The overall number of stained neurons in UC cortex was higher as compared to contralateral gyrus, suggesting the presence of axonal sprouting. The study shows that epileptogenesis is accompanied with global morphological changes in neocortical circuitry, which can be the cause of abnormal hyperexcitability and synchronous discharges observed during epilepsy.

1-C-91 Real time imaging of nestin signals in the injured brain

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Introduction:Neuroinflammation occurs due to hypoxia,ischemia and to a number of bacterial and viral infections. The inflammatory process in the neurogenic regions of the brain alters the microenvironment of the neural stem cells and thereby influences the fate of Neural Progenitor Cells. The mechanisms, function and significance of the modulation of neurogenesis during inflammatory processes remain to be elucidated. To address these questions we generated a transgenic mouse model in which we can visualize the process of induction of nestin signal in NPGs from the brain of live animals using biophotonic/bioluminescence imaging. Methods: Nestin-luc-GFP mice were subjected to 90 minutes of MCAO followed by a reperfusion period of 3,7d and 14 days. To elucidate the role of chronic neuroinflammation, Lipolysaccharide 5mg/kg body weight was injected to mice by intraperitoneally every 3 days until 14 days. Results: In the acute CNS injury model we observed the upregulation of nestin bioluminescent signal at 24hrs, 3 days and 7 days following the surgery. Chronic administration of LPS produced an upregulation of nestin signal at 24 hrs and gradually declines after 72hrs and reached the baseline level at 14 days. Histological analysis of the brain sections 72 hrs and 7 days after stroke shows an increase of nestin and the nestin-driven GFP transgene expression in GFAP and DCX positive cells. Conclusions: The presented reporter mouse represents a valid model to study effects of inflammation/ brain injury on in vivo dynamics of nestin induction and the fate of nestin expressing cells.

1-C-92 Early and late increases in neuronal sodium concentrations during post-traumatic epileptogenesis

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We have shown that post-traumatic accumulation of intracellular Cl results in a shift in the action of GABA from hyperpolarizing to depolarizing. This leads to reduced inhibition, enhanced propagation of neuronal firing, and may contribute to early post-traumatic seizures. Charge balance dictates that traumatic increases in intracellular Cl may be accompanied by an increase in cations, which could underlie cytotoxic edema and accompany epilepsy. We tested for changes in intracellular cation concentration, beginning with Na. Acute hippocampal slices and organotypic hippocampal slice cultures were prepared from wild-type C57BL/6J mice and incubated with the Na-sensitive dye SBFI (10µM). Two-photon imaging was used to achieve ratiometric determination of the intracellular Na concentration. In acute slices, intracellular Na was highest near the cut surface of the slice, and lowest in the deepest neurons. This indicates that trauma results in significant increases in intracellular Na. In organotypic slice cultures, [Na]i returned to low levels 3-4 days post-trauma. As the slices aged further, [Na]i then increased to levels comparable to those seen immediately post-trauma. Further, the application of 1µM of the fast Na channel inhibitor tetrodotoxin caused a decrease in [Na]i, whereas the application of 10µM of the Na/K ATPase inhibitor ouabain caused an increase in [Na]i. The dependence of [Na]i on action potentials and active Na export suggests that activity-dependent Na influx exceeds export capacity in a large subpopulation of neurons during epileptogenesis.

1-C-93 Differential phenotypes and functions of infiltrating macrophages and resident microglia after spinal cord injury

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Macrophages in the injured spinal cord arise from resident microglia and infiltrating, peripherally derived monocytes. It is still not clear if macrophages derived from these two populations differ in their roles after spinal cord injury (SCI). The aim of this study was to investigate the contribution to the phagocytic response and the clearance of damaged axons by macrophages derived from resident microglia in comparison to macrophages of a peripheral, blood-borne origin. The LysM-eGFPki transgenic mouse tags haematogenous macrophages, but not microglia, and allows the study of these two previously indistinguishable cell populations without the need for chimeric experiments. Using a combination of immunofluorescence, flow cytometry and neuronal tracing techniques our preliminary data have shown that microglia contact damaged axons early (24 h) after SCI and are the predominant macrophage to contain phagocytic material at 3 days. Thereafter, infiltrating macrophages become the predominant cell in contact axons and contain more phagocytic material. In addition, macrophages present a different set of polarization markers, dependent on their origin. We have also identified a population of Ly6C resident microglial macrophages, usually thought to be expressed only in hematogenously derived cells. These data highlight the differential roles played by macrophages, depending on their origin, and provide further information for cell specific targeting of inflammatory response after SCI.

1-C-94 Volume-Regulated Anion Channel (VRAC) Blocker DCPIB Has Neuroprotective Effects in Mouse Neontal Hypoxic-Ischemic Injury Model

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Perinatal and neonatal hypoxic-ischemic brain injury often leads to acute mortality and chronic

neurological morbidity in infants and children. Swelling-induced mediation of volume-regulated chloride channels is thought to be one of the non-glutamate mechanisms in cerebral ischemia, and CIC3 channel has been proposed as one of the candidates for VRACs. This study evaluates the importance of these channels in neonatal hypoxic-ischemic injury model using a specific VRAC blocker DCPIB. The cerebral hypoxic-ischemic injury was induced in postnatal seven-day-old P7 mouse pups. The mice which were treated with the blocker showed a significantly reduced mean percentage of affected hemispheric corrected infarct volume compared to the vehicle-treated mice. The treatment with DCPIB also improved functional recovery, as was evident by increased activity of blocker-treated group compared with vehicle-treated control group. Additionally, this study provides supportive evidence of the ability of DCPIB to significantly block VRAC mediated cell death in vitro in PC12 cell line under oxygen-glucose deprivation conditions by comparing intracellular chloride ion concentrations in cells treated with DCPIB and control group. These experiments demonstrate the pathophysiological role of VRACs in ischemic brain injury, and suggest the blocker as a potential, easily administrable therapeutic drug targeting VRACs in the context of perinatal and neonatal hypoxic-ischemic brain injury.

1-C-95 Cytoprotective effects of FTY720 in the Central Nervous System

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FTY720 is an approved agent for the treatment of multiple sclerosis (MS) that readily accesses the CNS. FTY720 binds S1P receptors (S1Pr), which are expressed by neuronal and glial cells in the CNS. The fate of S1Pr differs following binding of FTY720 or of its natural ligand. When bound by S1P, the receptor is internalized and recycled onto the cell membrane. When FTY720 binds to S1Pr, the receptor-ligand complex is internalized and then targeted to the endosomal compartment. The internalized receptors continue to signal resulting in active cellular responses. FTY720 can maintain persistent signaling via internalized S1P1r. We propose that during MS progression or inflammatory challenge, ER stress in astrocytes leads to increased ER Ca2 release, which subsequently leads to activation of store operated Ca2 entry (SOCE) and build-up of intracellular Ca2 . Consequently, increased intracellular Ca2 reverses mechanisms that sequester glutamate, resulting in glutamate exocytosis. By studying the transcriptome signature of FTY720 in human astrocytes, we have obtained evidence that FTY720 increases expression of a subset of Ca2 regulating proteins, which reduce ER Ca2 efflux and inhibit SOCE. We predict that this will prevent the reversal of glutamate re-uptake and limit NO production, thereby reducing neuronal excito-toxicity and mitochondrial damage in axons. We propose that the application of FTY720 protects astrocytes from Ca2 induced excito-toxicity, while facilitating neuronal and oligodendroglial protection, and preventing axonal loss.

1-C-96 Alpha-synuclein fibril formation and localization are affected by S129 phosphorylation

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α-Synuclein (α-syn) is a highly abundant presynaptic protein that exists as membrane-bound and freely-diffusible cytosolic. In normal brains, less than 5% of α-syn is phosphorylated at serine residue 129 (pS129), whereas nearly 90% of the α-syn in Parkinson disease Lewy bodies (LB) is phosphorylated at S129. To further clarify the relationship between S129 phosphorylation and the biophysical and biological properties of α-syn, we generated recombinant α-syn with and without pS129. To do this, we used E. coli to express human α-syn with and without polo-like-kinase 2 (PLK2), a major kinase responsible for S129 phosphorylation. High-performance liquid chromatography (HPLC) and western blot analyses revealed complete S129 phosphorylation when α-syn and PLK2 were co-expressed versus the absence of pS129 when α-syn

was expressed alone. Fibril formation of non-phosphorylated and phosphorylated forms of α-syn were then assessed by electron microscopy. Our results suggest that serine phosphorylation accelerated fibril formation. Moreover, the presence of PD-linked mutations, A53T and A30P, further increased the fibril formation of the pS129 α-syn. We also assessed whether pS129 affected the binding of α-syn to synaptosome membranes. Although, S129 phosphorylation had little effect on the WT and A53T α-syn membrane binding, it appeared to increase association of A30P α-syn. Overall, our results indicate that aberrant S129 phosphorylation modifies α-syn structure and fibril formation, and differentially impacts α-syn mutant binding to presynaptic membranes and cell localization.

1-C-97 Impaired GABAA receptor alpha2 subunit targeting result in seizures

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Neuronal activity is limited via the activation of γ-aminobutyric acid type A receptors (GABAARs), which are widely recognized as the principle mediators of fast synaptic inhibition. During the development of the nervous system inhibitory synapses containing GABAARs are formed on the axon-initial segment (AIS), cell bodies and dendrites of neurons. Synapses on these unique subcellular compartments are enriched with distinct subtypes of GABAARs comprised of differing subunit combinations. Specifically, synapses on the AIS contain α2 subunits while those on dendrites are enriched in α1 subunits. Differential subcellular targeting imparts unique properties to GABA-mediated currents at these distinct synapses. However the role that these distinct populations of inhibitory synapses play in coordinating neuronal activity and limiting epiletogenesis remains unknown. To directly examine this, we have created a knock-in mouse (Gabra2-1) in which the targeting of the α2 subunit to the inhibitory synapses on the AIS has been prevented, leading to inappropriate clustering. Despite mislocalization, we observe an increase in the total expression of α2, which is paralleled by an increase in the amplitude of miniature inhibitory postsynaptic currents in Gabra2-1 mice. Hetero- and homozygotes for this mutation are viable up to postnatal days 10-24 when they begin to display seizures and premature death. Collectively our findings provide mechanistic insight into how deficits in the formation of inhibitory synapses contribute to pediatric epilepsies.

1-C-98 Defective synaptic transmission at the NMJ in a zebrafish model of the FUS gene in ALS

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Mutations in the gene fused in sarcoma (FUS) have been shown to be associated with Amyotrophic Lateral Sclerosis (ALS). ALS presents clinically in adulthood and is characterized by the loss of motoneurons in the spinal cord and cerebral cortex. Animal models of the disease suggest that significant neuronal abnormalities exist during preclinical stages of the disease. The pathophysiological deficits causing impairment in motor function as a result of mutant FUS are unknown. To investigate this we expressed the wild type human gene (wtFUS) or the ALS-associated mutation R521H (mutFUS) in zebrafish larvae and characterized their motor (swimming) activity and function of their neuromuscular junctions (NMJs). Additionally, we tested knockdown of zebrafish fus with antisense morpholino oligonucleotide (fus AMO). Expression of either mutFUS or fus AMO resulted in greatly impaired swimming, reduced synaptic fidelity across the NMJ and reduced quantal transmission. These impairments in neuronal function could be partially restored in fus AMO larvae also expressing wtFUS (fus AMO wtFUS) but not mutFUS (fus AMO mutFUS). These results implicate both a loss and gain of FUS function which have specific neuronal consequences at the NMJ.

1-C-99 Voluntary exercise increases adult neurogenesis and improves cognitive function in a mouse model of Alzheimers disease.

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Alzheimer's disease (AD) is a neurodegenerative disorder accompanied by a progressive loss of neurons leading to cognitive impairment. Additionally, adult neurogenesis, normally contributing to learning and memory, is impaired in AD. Several non-invasive treatments are being developed to promote neuronal development, survival and function. For example, exercise promotes adult neurogenesis, synaptic plasticity, and cognition in animal models. In healthy adults and AD patients, exercise has been shown to have potential benefits on cognitive functions. The global effects that exercise has on those factors are not fully understood and they are the focus of this study We evaluated the effects of moderate voluntary exercise on cognition, neurogenesis, and plaque burden by giving mice access to running wheels for 1 and 2 months and assessing their functional recovery. We used an AD mouse model of amyloid pathology and their non-transgenic littermates as control. Our results show an improvement in hippocampal-dependent memory in transgenic mice exercising for 2 months compared to non-running transgenic mice. Transgenic exercising animals also exhibited significantly greater levels of hippocampal adult neurogenesis, as demonstrated by the increase of cells containing markers for cell proliferation and mature neurons. Plaque burden was not statistically different in the hippocampus of running compared to non-running mice We conclude that physical voluntary exercise has the potential to improve adult neurogenesis and cognition even in presence of amyloid pathology.

1-C-100 A BAC-transgenic mouse line overexpressing the co-chaperone and prion protein ligand STI1

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Stress inducible phosphoprotein 1 (STI1) is a 60 kDa co-chaperone that co-ordinates the formation of the Hsp70/Hsp90 heterocomplex involved in client protein folding and cellular stress responses. STI1 is also secreted from astrocytes via exosomes and triggers neuronal signalling following interaction with the cellular prion protein (PrPC). The interaction of STI1 and PrPC has been implicated in various processes including neuritogenesis, both long-term as well as short-term memory, neuroprotection and cell survival. Elimination of STI1 gene is not lethal in yeast and nematodes, but affects embryonic survival in mice. In order to understand the neuroprotective roles of STI1 in vivo we have generated a BAC transgenic mouse line (STI1-TgA) containing 8 extra copies of the STI1 gene. mRNA analysis showed a 6-fold increase in mRNA levels and Western blot analysis indicated a 4-fold increase in protein levels. To test if overexpressed STI1 in the STI1-TgA is functional we crossed this mouse line with STI1 heterozygous mice (STI1-/) and then intercrossed their progeny. Although STI1-/- mice did not survive, the expression of the STI1 BAC rescued the embryonic lethality in STI1-/- TgA mice. Studies on expression levels of STI1 interacting proteins in STI1TgA showed increased levels of Hsp90, indicating a possible influence of STI1 overexpression on the chaperone machinary. The STI1 TgA mice showed no behavioural abnormalities and their ability to learn were comparable to wild types. Future experiments will help to study neuronal protection by STI1 overexpression.

D – Sensory and Motor Systems

1-D-101 Measuring cognitive-motor integration in preclinical Alzheimer's disease: A discriminant analysis and investigation of neural correlates

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The objectives of our research are 1) to characterize how the ability to integrate cognition into action is disrupted by Alzheimer's disease (AD) in its early stages and 2) to examine the neural correlates of impaired cognitive-motor integration in preclinical AD. We propose that measuring visuomotor integration under conditions that place demands on visual-spatial and cognitive-motor processing may provide an effective behavioural means for the early detection of underlying Alzheimer's-type neuropathology. To this end, we have tested participants both with and without AD risk-factors on four visuomotor transformation tasks. Comparisons between at-risk and healthy control groups revealed significant performance disruptions in the at-risk group on the most difficult task. A discriminant analysis resulted in an overall classification accuracy of 90.2%. We suggest that the impairments observed in at-risk participants may reflect early neuropathology disrupting the intricate reciprocal communication between parietal and frontal brain areas required to successfully prepare and update complex reaching behaviours, and thus may serve as a functional biomarker for the underlying disease. Currently, we are examining the underlying neural anatomy and connectivity in relation to AD risk and cognitive-motor integration performance in these participants. To date, four at-risk participants and four age-matched controls have undergone anatomical, diffusion weighted, and resting-state functional connectivity scans. Preliminary analysis of this brain imaging data will also be presented.

1-D-102 Neurogenesis and growth factors expression after complete spinal cord transection in Pleurodeles waltlii

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Following spinal lesion, connections between the supraspinal centers and spinal neuronal networks can be disturbed, which causes the deterioration or even the complete absence of sublesional locomotor activity. In Mammals, possibilities of locomotion restoration are much reduced since descending tracts either have very poor regenerative ability or do not regenerate at all. However, in lower Vertebrates, there is spontaneous locomotion recuperation after complete spinal cord transection at the mid-trunk level. This phenomenon depends on a translesional descending axon regrowth originating from the brainstem. On the other hand, cellular and molecular mechanisms underlying spinal cord regeneration and in parallel, locomotion restoration of the animal, are not well known. FGF-2 plays an important role in different processes such as neural induction, neuronal progenitor proliferation and their differentiation. Studies have shown an over expression of this growth factor after tail amputation. Nestin, a protein specific for intermediate filaments, is considered as a neuronal precursor early marker. It has been recently shown that its expression increases after tail transection in Urodeles. Using this marker and in situ hybridization, our results show that the increase in the number of FGF-2 and FGFR2 mRNAs is correlated with an increase in Neurogenesis especially in the central canal lining cells immediately after lesion. This study also confirms that axonal regrowth through the lesion site initially follows a rostrocaudal direction.

1-D-103 Spatio-temporal selectivity of contrast adaptation in mouse primary visual cortex

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Prolonged viewing of high contrast gratings alters perceived stimulus contrast, and produces characteristic changes in the contrast response functions of neurons in the primary visual cortex (V1). This phenomenon is referred to as contrast

adaptation. Although contrast adaptation has been well studied, the neural mechanisms underlying this phenomenon are not well understood. Therefore, we investigated contrast adaptation in mouse V1 with the goal of establishing a quantitative description of contrast adaptation in a genetically manipulable animal model. One interesting aspect of contrast adaptation that has been observed both perceptually and in single unit studies is its specificity for the spatial and temporal characteristics of the stimulus. Using protocols that were readily comparable with previous studies in cats and primates, we found that contrast adaptation in mouse V1 neurons depended on the spatial and temporal frequency of the adaptor. Furthermore, we also used a novel contrast ramp stimulus that characterized the spatial and temporal specificity of contrast adaptation simultaneously. We found that for most mouse V1 neurons there was a slight difference between the peak in the spatio-temporal domain and the grating where adaptation was most pronounced, such that adaptation was usually stronger at higher spatial frequencies.

1-D-104 1 Hz repetitive transcranial magnetic stimulation over dorsal premotor cortex enhances offline motor memory consolidation for sequence-specific implicit learning

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Motor memories associated with skilled practice can be consolidated both during practice (online consolidation) and after practice (offline consolidation). This study investigated the role of dorsal premotor cortex (PMd) in early offline motor memory consolidation of implicit sequence-specific learning. Participants (n=33) were assigned to one of three groups of repetitive TMS over left PMd (1 Hz, 5 Hz or control) immediately following practice of a novel continuous tracking task. There was no additional practice following application of repetitive TMS. This procedure was repeated on 4 separate days. The tracking task contained a repeated sequence that could be learned implicitly and random sequences that could not. On a fifth day, implicit motor learning of the task was assessed using a retention test. We found that tracking error was decreased for the group who received 1 Hz repetitive TMS over PMd immediately following practice compared to control or 5 Hz repetitive TMS groups. Enhanced learning with 1 Hz repetitive TMS following practice was due to enhanced early offline consolidation and not differences in online learning between the groups within practice days. A follow-up experiment verified that stimulation of PMd following practice did not significantly change motor cortex excitability, suggesting that changes in offline consolidation can indeed be attributed to stimulation-induced changes in PMd. These findings support a differential role for PMd in online versus offline sequence-specific learning and offer converging evidence for competing memory systems.

1-D-105 Role for the striatal mammalian target of rapamycin (mTOR) proteins in the learning of a skilled motor task in mice

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This study investigated the implication of mTOR in the learning processes associated with the accelerating rotarod task in mice. Performances of mice on the rotarod, which accelerates from 4 to 40 rpm in 300s, were evaluated for 10 trials/session on day 1, 2 and 3. We observed a rapid improvement in performances within the first training session at day 1 and a slower progression in the following sessions that reached a plateau at day 3. Using the Western blot, levels of mTOR and its phosphorylated form at serine 2448 were measured at day 1, 2 and 3 in the striatum, hippocampus, cerebellum and cortex of trained mice. Rotarod learning did not affect mTOR levels in any of the regions, but induced an increase of phosphorylated mTOR in the hippocampus and striatum at day 1. Pharmacological inhibition and genetic knockdown of mTOR were performed in the

dorsal striatum. No difference between control and treated mice was observed in both treatment at day 1. However, performances were significantly decreased at day 2 and 3, suggesting motor learning deficiencies. To verify that the reduced performances were not due to impaired motor capacities, we performed the wire suspension and pole tests. We observed no difference between groups. Our data suggested that pharmacological inhibition and genetic knockdown of mTOR were selectively affecting motor learning in the dorsal striatum, but not movement executions. In addition, they showed that activation of mTOR was important for the long-lasting reorganization of striatal circuits during the memorization of a complex motor task.

1-D-106 Antinociceptive effects of spinal glutamate transporter inhibitors and membrane permeable metabotropic glutamate antagonists in rats with persistent hind paw inflammation

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Group I metabotropic glutamate receptors (mGluRs) are a class of excitatory G-protein coupled receptors present in the spinal cord dorsal horn (SCDH) where they have a well-established role in pain. Specifically, activation of these receptors has been implicated in central sensitization leading to chronic pain states. In addition to their well-known location on the cytoplasmic membrane, our lab has found evidence of these receptors intracellularly on the nuclear membrane in the SCDH of rats with chronic pain. Previous research has demonstrated that nuclear mGluRs in neurons cultured from brain tissue are functional receptors that bind glutamate entering the cell through the neuronal glutamate transporter (GT), EAAC1. Our objective is to determine the functional role of nuclear mGluRs in the SCDH in rats with persistent inflammatory pain. Here we show that pretreatment with EAAC1 inhibitor, L-β -threo-benzyl-aspartate, attenuates glutamate-induced nociceptive behaviours in rats with inflammatory pain (hind paw injection of complete Freund's adjuvant (CFA)). Further, pretreatment with cell permeable group I mGluR antagonists, CPCCOEt and fenobam, but not cell impermeable group I mGluR antagonist, LY 395053, attenuates glutamate-induced nociceptive behaviours in CFA rats. Blocking glutamate transport into neurons using EAAC1 inhibitors as well as blocking intracellular mGluR activation using cell permeable mGluR antagonists attenuates glutamate-induced pain behaviours in CFA rats, providing preliminary empirical support for a functional role of SCDH nuclear mGluRs in pain.

1-D-107 Changes in short-latency afferent inhibition in hand muscles during movement preparation

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Somatosensory input inhibits primary motor cortex (M1) output at ~ 20-25ms following peripheral nerve stimulation, an effect known as short-latency afferent inhibition (SAI). The purpose of this study was to determine how SAI is modulated during movement preparation of either 2nd or 5th digit movement. Participants were required to perform the reaction time task in the presence of a "warning" and "go" cue. The content of the warning cue indicated whether to perform 2nd digit or 5th digit flexion. A Transcranial magnetic stimulation (TMS) pulse was delivered alone over M1 "hotspot" for the first dorsal interosseous (FDI) muscle of the right hand and motor evoked potentials were recorded (unconditioned MEP). To test for SAI, the cutaneous nerve of the index finger was stimulated 25 ms before the single TMS pulse and the resultant MEP was recorded in FDI (conditioned MEP). 10 unconditioned and 10 conditioned MEPs were obtained either at rest or at one second after the warning cue when the participant was preparing to perform 2nd digit or 5th digit movement. Preliminary data (n = 5) suggests that during movement preparation somatic inputs cause a change in M1 from inhibition to facilitation

regardless of whether the 2nd or 5th digit is about to perform the task. These data could indicate that the relevancy of the somatic inputs to the task may not be driving the changes in M1 excitability during movement preparation and instead the changes are non-selective to the digit involved.

1-D-108 Cross-modal hemodynamic activity in non-primary areas of deaf cat auditory cortex

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External inputs received through the sensory organs early in development help to establish sensory maps in the brain. When the developing brain is deprived of a specific sensory experience, evidence suggests that the deprived cortical region is recruited to participate in processing other sensory stimuli. In the auditory system, several studies have reported visually-evoked activity within auditory cortex in the deaf. We seek to use functional magnetic resonance imaging (fMRI) to characterize the hemodynamic responses associated with this cross-modal activity in the auditory cortex of deaf cats. We acquired functional images in adult (> 6 months) early-deafened cats under anesthesia (ketamine/isoflurane) during the presentation of moving grating patterns using a 7T MRI scanner. Full-field high-contrast square-wave bi-directional horizontally or vertically moving bars (spatial frequency: 0.15 cycles/°) were projected onto a target screen (27 cm × 20 cm) at a viewing distance of 50 cm. We presented the grating patterns at speeds of 0.5 Hz, 2 Hz and 8 Hz in a block design interleaved with baseline (gray screen) blocks. Visually-evoked cross-modal activity was primarily observed in the secondary auditory field (AII), the dorsal zone (DZ) and the posterior auditory field (PAF) with a bias towards the right auditory cortex in deaf cats. No visually-evoked responses were evident in these areas in hearing controls. Our results support previous findings which implicate higher-order non-primary auditory fields as sites of visual reorganization in deaf auditory cortex.

1-D-109 Unilateral inactivation of frontal eye fields decreases visual, delay, and saccadic activity in intermediate superior colliculus

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Despite the frontal eye fields (FEF) and intermediate layers of the superior colliculus (iSC) being two of the most intensively investigated oculomotor structures, the functional contribution of the FEF to activity within the iSC has never been directly addressed. Here we couple reversible cyrogenic inactivation of FEF with neurophysiological recordings in the iSC to examine how responses of iSC neurons are influenced by the removal of a main cortical input. Monkeys were required to generate saccades to remembered or persistent visual cues into or opposite of an isolated neuron's response field before, during, and after unilateral FEF inactivation. In two monkeys studied thus far, we found decreases in all components of the sensorimotor response in the ipsilesional iSC neurons, although greater proportions of neurons having delay and saccadic activity were affected than those containing visual activity. Within neurons possessing at least two of the three responses, we found that the decrease in one response component did not necessarily predict the decrease in the other component. Finally, we observed no consistent changes to sensorimotor activity in the contralesional iSC in any component. While our results are largely consistent with the information conveyed along direct corticotectal neurons identified through anti-dromic identification, future studies employing bilateral cryogenic FEF inactivation are needed to differentiate whether the changes we have observed are secondary to biases in visuospatial attention.

1-D-110 Distinct single unit activity between rostral and caudal dorsal premotor cortex during complex visuomotor control.

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The planning and execution of visually-guided reach movements has become more complex as we have evolved to use tools. Tool-use typically requires a spatial decoupling between gaze direction and hand orientation in order to successfully interact with the object of interest. Here we examine the role of the premotor cortex in this behaviour. The goal of this study was to characterize the neural activity from two rhesus macaques within the caudal and rostral subdivisions of the dorsal premotor cortex (PMdr and PMdc) when going from the most basic reaching movement (direct interaction) to one that involves a simple dissociation between the action of the eye and hand (eye-hand decoupled). Similar to our previously reported LFP results, we observed distinct task-related differences as well as topographical differences between the single cell activity of PMdr and PMdc. Our results suggest functional differences between PMdr and PMdc during visually-guided reaching. PMdr showed enhanced activity during the early planning of a decoupled reach, when the integration of the rule-based aspects were occurring. PMdc is more active during the late planning and early movement phase of a decoupled reach when the reliance on proprioceptive feedback and online control would be important. More broadly, our results highlight the necessity of accounting for the non-standard nature of a motor task when interpreting movement control research data.

1-D-111 Core Auditory Cortex Of The Cat Revealed Using High-Field FMRI

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Tonotopy is a spatially ordered frequency distribution within an acoustic structure. Classically, Tonotopy has been demonstrated using single-unit electrophysiological recording techniques.. Previous electrophysiological investigations in the cat have revealed tonotopy in primary auditory cortex (A1), the anterior auditory field (AAF), the posterior auditory field (PAF) and the ventral posterior auditory field (VPAF). Functional magnetic resonance imaging (fMRI) has been used to demonstrate tonotopy in auditory cortex of humans and monkeys. Tonotopy is characteristic of core auditory areas, but not higher-order processing areas. Therefore, we used fMRI to identify core auditory cortex in the cat. We used a 7T MRI scanner to identify primary, or core, auditory cortex of the cat. Eight tones, 1 kHz, 5 kHz, 10 kHz, 13 kHz, 16 kHz, 17 kHz, 20 kHz and 30 kHz, were presented along with a broad band noise (BBN) in a block design interleaved with baseline blocks in which no stimulus was presented. Tonotopy was successfully identified in both A1 and AAF. A similar tonotopy could not be identified in PAF or VPAF. The strongest activations by a BBN were along the posterior ectosylvian sulcus corresponding to PAF and VPAF. This suggests that PAF and VPAF may be dedicated to processing more complex acoustic stimuli. The tonotopic organization of A1 and AAF, along with the selectivity of PAF and VPAF for BBN stimulation, indicates that the auditory "core" in the cat consists of A1 and AAF.

1-D-112 Cortical control of sensory information processing in the thalamus during slow oscillations

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During cortically generated slow oscillation cortical neurons alternate between active and silent states and recruit thalamus. Sensory information processing in the thalamus during slow oscillation remains largely unknown. In ketamine/xylazine anesthetized CD1 mice we recorded cortical LFP and intracellular activities of thalamic neurons. In first order nuclei (VPM, LGN) single or spindle-like IPSPs were observed during cortical active states. We did not detect any spontaneous burst firing in these nuclei. In higher order nuclei depolarization of thalamocortical cells were observed during active states maintained by EPSPs. Sensory stimulation (whiskers - air puff, eye - flash) elicited mixed IPSPs and EPSPs (evidently originating from ascending sensory pathways) in VPM and LGN neurons. The reversible blockade of the

somatosensory cortex by cooling disrupted the slow oscillation in VPM neurons, enhanced spindle-like series of IPSPs, and the inhibitory response elicited by whiskers' stimulation. In the higher order Po nucleus cooling of the cortex disrupted the slow wave pattern, transformed spontaneous activities into series of EPSPs generated with spindle frequencies, and enhanced excitatory response elicited by whiskers' stimulation. We suggest that higher-order thalamic nuclei may contribute to the generation of cortical active states during slow oscillation, while cortically controlled IPSPs in first order nuclei may contribute to setting up the thresholds for transmitting sensory volleys to neocortex during slow wave sleep. Supported by NSERC, CHIR, and FRSQ.

1-D-113 Effects Of Core Auditory Cortex Deactivation On Neuronal Response To Simple And Complex Acoustic Signals In The Contralateral Anterior Auditory Field

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Inter-hemispheric communication has been implicated in various functions of sensory signal processing and perception. Despite ample evidence demonstrating this phenomenon in the visual and somatosensory systems, to date, limited assessment of transcallosal transmission during acoustic signal processing has hindered our understanding of the functions performed by inter-hemispheric connections in the auditory system. Therefore, in an effort to further our understanding of acoustic processing in the cerebrum, the present investigation examines the impact of core auditory field deactivation on the response properties of contralateral anterior auditory field (AAF) neurons in the felis catus. Specifically, responses to simple (pure tones) and complex (noise bursts and FM sweeps) acoustic signals were measured across AAF neurons before, during, and after individual and combined deactivation of contralateral primary auditory cortex (A1) and AAF neurons. Single-unit recording techniques in combination with cooling deactivation methods were used to measure response variations during contralateral deactivation. Data analyses revealed that on average: (i) inter-hemispheric projections from core auditory areas to contralateral AAF neurons are predominantly excitatory, (ii) changes in response strength vary based on acoustic features, (iii) A1 and AAF projections can modulate AAF activity differently, (iv) decreases in response strength are not specific to particular cortical laminae, (v) contralateral inputs modulate AAF neuronal threshold levels.

1-D-114 Development of an animal model for the effects of Transcranial Magnetic Stimulation on the primate oculomotor system

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Transcranial magnetic stimulation (TMS) is a non-invasive technique to stimulate the human brain. Despite widespread use, a mechanistic understanding of its actions is lacking. We are developing a primate model of TMS over the frontal eye fields (FEF), using prior knowledge about the oculomotor system to better understand the mechanisms of TMS. As in humans, single pulses of TMS-FEF evoke a brief and rapid head turning synergy consisting of facilitation and inhibition of contralateral and ipsilateral turning muscles, respectively. While the evoked responses vary considerably day to day, they increase systematically with greater stimulation intensity and decrease as the TMS coil moves away from the FEF. The evoked response is also greater when TMS-FEF is delivered during behavioural task that recruits the stimulated FEF. The overall degree of similarities between results in humans and monkeys is encouraging for the development of an animal model, and motivates predictions which can be tested directly by combining TMS-FEF with neurophysiological recordings downstream of the FEF to record altered neural activity.

1-D-115 Altered topography of corticothalamic and corticotectal projections in enucleated and anophthalmic mice

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Corticothalamic and thalamocortical projections exhibit an initial gross topographic organisation that is established by molecular guidance cues and further refined by activity related mechanisms. Thalamocortical projections from the lateral geniculate nucleus (LGN) to the primary visual cortex (V1) are initially diffuse and refined during the first postnatal week. The superior colliculus (SC) receives topographic projections from the retina and from the visual cortex. There is evidence that spontaneous retinal activity directs convergence of retinal and cortical projections to the SC. Both retinal projections and prenatal spontaneous patterned activity might be contributing factors for the topographic organization of corticothalamic and corticotectal projections. METHODS: The topography of corticothalamic projections to the LGN and lateroposterior nucleus and of the corticotectal projection was studied in intact and enucleated C57Bl6 mice and in ZRDCT anophthalmic mice. Two anterograde tracers, BDA and Phal, were respectively injected in the anterior and posterior V1 and were visualized with fluorescent probes. RESULTS: There was a greater overlap and extent of labelling in the anophthalmic mice than in the enucleated mice. Corticothalamic projections were more focused in the intact than in blind mice. Corticotectal projections were more dispersed in anophthalmic than in enucleated mice. CONCLUSION: Retinal projections and prenatal spontaneous patterned activity appear to be required for the refinement of corticothalamic and of corticotectal topographic projections.

1-D-116 Influence of primary auditory cortex and the posterior auditory field on neuronal responses in the dorsal zone of cat auditory cortex

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Hierarchical processing schemes for auditory cortex have been proposed based on anatomical cortical and thalamic connections, however, the functional nature of this network remains largely unexplored. A series of studies has previously addressed functional reciprocal connectivity between primary auditory cortex (A1) and the anterior and posterior auditory fields (AAF and PAF) and second auditory cortex (A2) using cortical cooling deactivation; thus, the purpose of the present study was to expand this functional assessment of inputs to a higher-order auditory area, the dorsal zone (DZ). Cooling loops were placed over areas A1 and PAF based on electrophysiological mapping (A1) and known sulcal and gyral landmarks (A1 & PAF), because they comprise the two largest auditory inputs to DZ. Because both A1 & PAF occupy lower positions within proposed models of auditory cortical hierarchy, it was expected that deactivation of these areas would significantly influence neuronal response rates in DZ. Broadband noise stimuli were played at 65 dB while A1 alone, PAF alone, and both A1 and PAF were reversibly deactivated using cortical cooling, and neuronal responses in DZ were recorded. Cooling A1 and PAF individually or combined significantly reduced mean peak response rates in DZ. Together, these results support previous models of auditory cortical hierarchical organization, in that deactivation of the two largest auditory inputs (A1 and PAF) resulted in significant declines in neuronal response rates in DZ.

1-D-117 Evidence for the online cost to go: A rapid decision to avoid an obstacle

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Various studies on decisional processing use motor actions to reflect the outcome of a decisional process, suggesting a serial framework. This dissociation between decision and control contrasts with the flexible feedback control strategies expressed in many behavioral contexts. In the present study, we investigate how feedback influences decisional processing during ongoing movements using an obstacle avoidance task.

Subjects performed reaching movements between two spatial targets with obstacles located just to the sides of a direct path between the two targets. On random trials, we perturbed the limb with one of four mechanical loads. Notably, the medium-sized leftward perturbation led to two different strategies, with some trials directed between the obstacles and other trials to the left of the obstacles. Importantly, changes in muscle activity between these strategies were observed in less than 60ms post-perturbation without vision of the limb. We found that small variability in hand position before the motor response predicted the subsequent movement strategy, as also observed for optimal feedback control models where the decision is based on the expected remaining costs associated with each strategy (i.e. present cost-to-go). We suggest that this class of motor decision is generated within the motor control policy that considers potential ways to attain a behavioural goal.

1-D-118 Neural networks implementing the visuomotor transformation for smooth pursuit

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To generate spatially accurate smooth pursuit eye movements, the brain must account for eye and head geometries when transforming retinal target signals into motor commands to control the eyes. Here, we investigate how this visuomotor transformation could be performed neurally We created a physiologically-inspired four-layer feedforward neural network model to produce spatially correct smooth pursuit. An area MT-like retinal target position and velocity input was combined with both eye-in-head and head-on-shoulder position and velocity input signals. After training using a pseudo-Newton method with pre-conditioned gradient descent, the network model used extraretinal signals to generate spatially accurate pursuit (100 HLU network; 3D compensation analysis: slope (95%CI) = 0.801 (±0.009), R^2 = 0.745). To see how the network carried out this transformation, we simulated several experimental conditions and observed how HLU velocity tuning properties varied with extraretinal inputs, revealing that changes in eye and head inputs resulted in gain modulations and velocity tuning shifts in the HLUs (modulation gains from -1.40 to 1.31 and compensatory shift gains from -2.19 to 2.39). These HLU properties are qualitatively similar to electrophysiological recordings from MT and MST, areas theorized to be involved in the visuomotor transformation for smooth pursuit. Thus, our model provides a mechanistic explanation for the presence of extraretinal signals in these areas and suggests that they could perform this transformation using feedforward computations.

1-D-119 Duration of Acoustic Experience Shapes Development of Auditory Cortex Cartography

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Sensory input is essential for the functional development of the cerebrum. A lack of acoustic experience in deaf individuals impairs maturation of auditory circuits and structures. Auditory cortical areas are differentially affected in cats deafened shortly after birth versus cats deafened in adulthood. Interestingly, the total volume of auditory cortex is positively correlated to the age of deafness onset, such that auditory cortex is more diminished in cats deafened early in life. To further understand the relationship between acoustic experience and cortical development, auditory cortex of congenitally deaf cats (CDC) was examined. In CDCs, a genetic defect causes inner ear degeneration during development, preventing any hearing experience. Cerebral cytoarchitecture was revealed immunohistochemically using SMI-32, a monoclonal antibody used to distinguish auditory areas in many species. Auditory areas were delineated in coronal sections and their volumes measured. Total auditory cortex volume was

significantly reduced in CDCs, supporting the correlation between auditory cortex volume and hearing experience. Posterior limits of caudal auditory areas were shifted anteriorly, suggesting expanded visual cortex. Furthermore, a novel area with uniquely light SMI-32 labeling was discernible from the strongly immunoreactive anterior auditory field and adjacent somatosensory cortex. This new area may reflect underlying crossmodal plasticity following congenital deafness. Overall, this study demonstrates the importance of acoustic experience on shaping auditory cortex cartography.

1-D-120 Predictive control in bimanual limb movements

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Simple movements we make in everyday life are the result of complex transformations that predict the sensory consequences of the intended motor output. To examine this interaction, we have characterized how motor planning can influence temporal perception. This was accomplished by applying vibrotactile stimuli to each hand in human subjects during the planning stages of an arm-crossing or uncrossing movement to investigate how temporal order judgements (TOJ) are systematically influenced. We have previously shown that planning to cross or uncross the arms induces a subjective reversal of spatially-defined cutaneous TOJs. In the present experiment, we investigated how the extent to which the hands will subsequently be crossed or uncrossed influences TOJ error rates. We had subjects plan to move to 4 different targets that would leave the hands crossed or uncrossed by varying degrees. We were able to demonstrate that even though cutaneous stimuli were applied before the movements, if subjects were planning on moving into a more completely crossed or uncrossed configuration, TOJ errors changed more markedly. This data suggest the brain uses planning signals to predict sensations from impending movements.

1-D-121 GDNF Regulation In An In Vitro Model Of Denervated Muscle

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Muscle-derived glial cell line-derived neurotrophic factor (GDNF) levels are up-regulated in denervated skeletal muscle and return to normal following re-innervation, supporting a role for GDNF in promoting survival of skeletal muscle and regeneration of injured nerves. However, the mechanism by which GDNF is regulated in denervated muscle is not well understood The nerve-derived neurotransmitter calcitonin gene-related peptide (CGRP), like GDNF, is up-regulated following neuromuscular injury. In this study, we show that CGRP functions to increase GDNF levels in differentiated rat myotubes. We found that CGRP treatment increased secreted GDNF protein without altering GDNF mRNA levels. Further, the addition of a translation inhibitor (cycloheximide) did not affect CGRP-induced GDNF protein levels, whereas addition of a secretional inhibitor (Brefeldin A) blocked the CGRP-induced increase in GDNF, demonstrating that CGRP increases the secretion but not the expression of GDNF protein. CGRP treatment also increased interleukin-6 (IL-6) and decreased ciliary neurotrophic factor (CNTF) protein secretion from rat myotubes. CGRP may regulate GDNF, IL-6 and CNTF secretion through a calcium-dependent mechanism in skeletal muscle, as CGRP is known to increase cyclic-AMP and activate protein kinase A. This study identifies a mechanism by which the secretion of muscle-derived GDNF is increased and also establishes a role for CGRP in promoting survival and regeneration following muscle denervation through the regulation of trophic factors.

1-D-122 Amplified Cortical, But Not Thalamic, Somatosensory And Visual Projections To The Anterior Auditory Field Following Early- Or Late-Onset Deafness

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Investigations of the cortical consequences of deafness show that secondary auditory cortical areas cross-modally reorganize to exhibit visual or somatosensory responsiveness. This reorganization may be related to the onset of deafness. However, recent studies have found that this plasticity is not restricted to secondary cortical regions, but can also be identified in core auditory areas. Specifically, in early-deaf cats, tactile and visual stimuli evoke activity in the anterior auditory field (AAF). The purpose of this investigation was to examine possible alterations in thalamic and cortical projections to AAF that may underlie the crossmodal plasticity identified following early-onset deafness. To accomplish this, we deposited a retrograde tracer (biotinylated dextran amine) in AAF of early-, late-deaf, and hearing cats (n=5 per group). We found that 1) compared to late-deafness, early-deafness results in a greater amplification of cortical somatosensory and visual projections to AAF, 2) following deafness, there is a greater amplification of somatosensory, than visual, projections to AAF, 3) the anterior ectosylvian visual area is the only visual area with amplified projections to AAF following deafness, 4) projections to AAF from primary auditory cortex and the dorsal zone decrease following both early- and late-onset deafness, and 5) thalamocortical projections to AAF were similar in both hearing and deaf subjects. In total, the results show that the deafness primarily alters cortical, but not thalamic, projections emerging from somatosensory and visual regions.

1-D-123 The temporal resolution of binding in area MT during motion-correlation perception

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Many studies have suggested two separate systems in visual motion processing: a low-level system that is passive and effortless (Lu and Sperling, 1996), and a high-level system that requires attention (Cavanagh, 1992; Battelli et. al 2001). The temporal resolution of high-level system is ~10 Hz, which is much lower than the temporal resolution of the low-level system at 30-50 Hz (Rovamo and Roninen 1984, Buracas et. al 1998). The goal of our experiment was to explore how motion-sensitive MT neurons encoded a rapidly and unpredictably changing stimulus when a subject binds together two moving visual stimuli. We trained three monkeys (Macaca mulatta) to perform a motion-correlation detection task using two non-overlapping patches of random dot motion. Upon fixation on a central point, the two patches moved independently with a Pearson's correlation of zero. The animals were required to release a lever when the motion pattern of the two moving patches became correlated. We recorded from 60 pairs of MT neurons (non-overlapping RFs) using two microelectrodes separated by approximately 1-3 mm. We found the temporal limit of predicting behavior for both the stimulus and neural responses was ~10 Hz. The spectral coherence between the stimulus and MT responses was the highest at ~10 Hz, but importantly showed no difference between correct and failed trials. Our results suggest that although area MT encodes a wide frequency range, frequencies above 10 Hz are not used by the rest of the brain when binding high-level motion stimuli.

1-D-124 Motor learning and sensory recalibration following adaptation to translated visuomotor perturbations in Parkinson's disease

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When faced with novel visuomotor perturbations, individuals adapt their movements and recalibrate their proprioceptive sense of hand position to match the visual estimate of their hand provided; that is, they begin to feel their hand where they see it. These processes require sensory integration that

have been suggested to depend on basal ganglia (BG) structures. To test the role of BG-cortical loops in proprioceptive recalibration following visuomotor adaptation, we examined these processes in patients with Parkinson's disease (PD). Thirteen mild to moderate PD patients and 14 age-matched healthy controls made reaching movements to visual targets while visual feedback of their unseen hand was gradually translated to the right of their actual hand. Analysis of aftereffect trials (completed without visual feedback) revealed that patients and controls adapted their reaches in a similar manner. Estimates of proprioceptive sense of hand position after training with aligned visual feedback revealed a small leftward bias. Although the biases of these hand position estimates did not differ between groups, their associated precision (uncertainty) was significantly larger in PD patients off medication than controls. Dopamine replacement did not reverse this deficit nor did it interfere with PD patients' intact adaptation and normal recalibration bias. Thus, PD patients are able to adjust their sensorimotor mappings to gradually introduced distortions, and recalibrate proprioception accuracy but not precision. Dopaminergic replacement had little effect on these processes.

1-D-125 Proprioceptive recalibration in Ehlers-Danlos Syndrome patients and healthy controls

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Reaching movements are rapidly adapted following training to rotated visual feedback of the hand (visuomotor adaptation).We have also shown that visuomotor adaptation results in changes in estimates of felt hand position (proprioceptive recalibration) in the direction of the visuomotor distortion (Cressman and colleagues, 2009, 2010).The goal of experiment one was to determine the influence of visuomotor adaptation on proprioceptive estimates of hand position versus proprioceptive-guided reaches. Following visuomotor adaptation, subjects recalibrated their felt hand position to a similar extent (~4˚ in the direction of the cursor rotation) in both tasks. However, these results were true only for proprioceptive-guided reaches to the adapted hand as reaches to body midline were not affected by adaptation. This suggests that proprioceptive recalibration is restricted to the adapted hand and does not generalize to the rest of the body. In experiment two we investigated proprioceptive acuity and proprioceptive recalibration in a group of individuals with Ehlers-Danlos Syndrome (EDS), a degenerative condition associated with collagen malformation. EDS patients were less precise in estimating their hand position in the peripheral workspace compared to healthy controls. Despite this poor acuity, recalibrated hand proprioception to the same extent as healthy controls. This is consistent with other populations who experience proprioceptive deficits (the elderly or Parkinson's patients), suggesting that sensory noise does not influence the extent of either motor or sensory plasticity.

1-D-126 Intermanual Transfer and Proprioceptive Recalibration Following Training with Translated Visual Feedback of the hand

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Reaching with visual feedback that is translated with respect to the actual hand's location leads to changes in reach trajectories (i.e., visuomotor adaptation). Previous studies have also demonstrated that when training to reach with misaligned visual feedback of the hand, the opposite hand also partially adapts, providing evidence of intermanual transfer. Moreover, our lab has shown that visuomotor adaptation to a translated cursor also leads to changes in felt hand position, what we call proprioceptive recalibration, such that subjects' estimate of felt hand position relative to both visual reference markers, and non-visual reference markers (e.g. body midline), shifts in the direction of the visuomotor distortion. In the present study we sought to determine if visuomotor adaptation and/or proprioceptive recalibration transfers from the trained hand to the untrained hand. We found intermanual transfer to

the left untrained hand after subjects trained their right hand to reach with translated visual feedback. Transfer from the left trained to the right untrained hand was not observed. Despite finding changes in felt hand position in both trained hands, we did not find similar evidence of proprioceptive recalibration in the right or left untrained hands. Taken together, our results suggest that unlike visuomotor adaptation, proprioceptive recalibration does not transfer between hands and is specific only to the arm exposed to the distortion.

1-D-127 Retention of proprioceptive recalibration following visuomotor adaptation

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We sought to evaluate whether changes in proprioception, following visuomotor adaptation, are sufficiently robust to be retained the following day (<24 hours). Our project builds on our laboratory's recent findings that motor learning not only leads to changes in movement, but to changes in proprioceptive sense of hand position as well. It has been shown that motor changes persist for extended periods of time; However, less is known about retention of sensory changes. The experiment consisted of two separate sessions, conducted 24 hours apart. While grasping the handle of a robot manipulandum, 36 subjects reached to various visual targets while their unseen hand was represented by a cursor that was either aligned with or was gradually rotated 45° CCW relative to hand location. Following each training task, subjects completed reaching trials without visual hand feedback in order to assess aftereffects, as well as a proprioceptive estimate task. Consistent with previous findings, subjects who significantly recalibrated their sense of felt hand position did so by approximately 5.7° rightwards following visuomotor adaptation. More importantly, even after 24 hours, this change in felt hand position persisted. Our results suggest that once subjects had adapted their reach to a visuomotor rotation, retention of sensory changes did indeed occur the following day.

1-D-128 Does a blind human expert echolocator show size constancy?

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Similar to bats and dolphins, some blind humans have developed the ability to use echoes to perceive their silent surroundings. By producing a clicking sound with their tongue, these individuals can listen for echoes reflected from objects and surfaces in their environment. These echoes contain information such as the size, shape, distance, and material properties of objects. This technique, then, operates as a crude substitute for vision, allowing human echolocators to 'see' silent objects at a distance, objects that would otherwise go undetected. Given this relationship between vision and echolocation, we were interested to see whether the echolocation of objects would, like vision, show size constancy. In vision, size constancy refers to the stable perception of the size of objects at different viewing distances despite the fact that, at these different distances, the same objects subtend a different visual angle on the retina. To investigate whether size constancy operates in echolocation, we had a blind expert echolocator 'click' toward objects of different sizes presented at different distances. The expert echolocator consistently identified the true physical size of the objects independent of viewing distance. Blind non-echolocators and blind-folded sighted controls did not show reliable size constancy in this situation, even though they were encouraged to clap and make vocalizations. Taken together, this evidence suggests that size constancy is not a purely visual phenomenon, but can operate via an auditory-based substitute for vision, such as human echolocation.

1-D-129 Reaching alters orientation responses and response variability in area V2 neurons

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The premotor theory of attention proposes that spatial attention is allocated through activation of neural motor circuits and has been shown within the oculomotor system. Recent evidence suggests that movements which place the hand near to-be-processed visual stimuli also improve visual processing. The hand speeds detection of nearby targets and slows the disengagement of attention. Simply planning to grasp a bar improves sensitivity to changes in its orientation. Also, stimulus detection and size perception are improved in near-hand space in blindsight and extinction patients. As there are separate target selection systems for the eye and the hand, motor control of reaching could potentially deploy attention to near-hand space. To determine if reaching improves visual processing, we recorded from 39 neurons in area V2 of 2 animals. We tested whether responses to task-irrelevant oriented bars were enhanced when the animals grasped a touchbar near to but outside the neuron's receptive field. Unlike oculomotor-driven spatial attention which results in gain modulation of neuronal responses, we found that reaching preferentially enhanced responses to the preferred orientation. This differential modulation results in sharpened orientation tuning in the space around the hand, which would improve grasping accuracy. We also found that reaching reduces visual processing response variability, a result consistent with feedback from motor control circuitry. Together these results suggest that the reaching and grasping networks deploy visual attention to near-hand space.

1-D-130 Velocity Sensitivity across Electrosensory Lateral line Lobe maps

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Sensory systems must often process stimuli whose spatiotemporal characteristics vary over a wide range. One coding strategy is to use multiple parallel topographic representations of sensory space to parse this vast range of attributes into smaller subsets. In the weakly electric fish Apteronotus leptorhynchus, specialized electroreceptors (P-units) sense amplitude modulations of self-generated electric organ discharge and project to three parallel topographic maps of the sensory epithelium within the hindbrain: centromedial (CMS), centrolateral (CLS), and lateral (LS) segments. Neural responses in these maps have been well characterized under stationary stimuli. Specifically, neurons within CMS/CLS/LS are preferentially tuned to low/mid/high frequencies. However, neural responses to moving stimuli have not been studied. We performed extracellular recordings from pyramidal neurons across maps in response to moving objects with different velocities. We calculated the velocity response profile (VRP) for two types of pyramidal cells (ON/OFF) within each map. Based on results obtained for stationary stimuli, one might have expected differential VRPs across the maps. Surprisingly, VRPs were similar across maps. To explain these results, we developed a model that includes the known center-surround receptive field structure and computed its response to a simulated moving object. We found including a delay for the surround region can give rise to the high pass VRP observed in experimental data. Further modeling studies are being conducted to test these predictions experimentally.

1-D-131 Disrupting the integration of a cognitive rule with a motor action in decoupled eye-hand coordination using a dual task paradigm

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Guiding a limb with peripheral vision, even in situations where one is free to foveate the visual target, can rely on the use of explicit cognitive rules (strategic control) or on the implicit recalibration of gaze and the decoupled limb position (sensorimotor recalibration). We previously demonstrated in a patient with optic ataxia (OA) having superior parietal lobule damage an increased reliance on explicit strategic control when

reaching under a 90° cursor feedback rotation condition. We observed that performance in OA improved when orienting a rotated cursor towards ordinal (on-axis) targets involving an explicit rule (up=right) relative to oblique (off-axis) targets involving a more implicit sensorimotor realignment. Here, to further differentiate the fundamental mechanisms of decoupled visuomotor control, we tested 20 healthy participants in a dual task. Participants counted backwards while simultaneously reaching with either veridical or rotated (90°) cursor feedback. By increasing overall neural load, the dual task served as a non-invasive means to disrupt the integration of a cognitive rule with a motor action. As predicted, in contrast to the results seen in OA, the increased neural load led to greater performance deficits during 90° rotation towards ordinal vs. oblique targets, implying a selective disruption of explicit control of decoupled visually-guided reaching. Our results suggest that independent neural pathways may underlie the control of these different types of reaching, since one class of movement was interfered with to a greater extent than the other.

1-D-132 Robotic assessment of limb afferent feedback for motor corrections post-stroke

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Our motor system has the ability to rapidly adjust to an unpredictable environment. For example, if bumped when holding a mug of coffee, we can rapidly adjust our arm's posture to avoid spilling. Stroke can damage sensory and motor regions of the brain leading to impairments of the upper limb such as difficulties responding to unexpected, yet functionally relevant, perturbations. We are exploring the use of robots to objectively quantify impairments in the use of sensory feedback to guide motor action post-stroke. Subjects with subacute stroke (n=28) and non-disabled controls (n=81) were assessed in a postural perturbation task using a KINARM exoskeleton robot. In each trial, subjects were required to maintain their hand at a central target and then a constant mechanical load was applied to the elbow or shoulder at a random time. Visual feedback of the hand was removed at perturbation onset. The behaviour of controls defined a normative range where performance outside the 95th percentile identified stroke-related impairments. Sixty-eight percent of subjects with stroke showed longer durations of deceleration away from the target. As well, 57% of subjects with stroke had larger endpoint errors than controls. Interestingly, stroke subjects showed bilateral deficits in deceleration duration and endpoint error in 36% and 46% of subjects, respectively. These robotic measures allow us to objectively quantify how quickly (deceleration duration) and accurately (endpoint error) subjects are able to use arm proprioceptive feedback for motor action.

E – Homeostatic and Neuroendoctrine Systems

1-E-133 Behavioural and Hormonal Measures of Anxiety in Response to Chronic and Acute Ethanol Exposure in Zebrafish, Danio rerio

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The zebrafish stress response utilizes cortisol, a hormone that also mediates the stress response in humans. Alcohol reduces stress and alters cortisol levels but the effect of prolonged exposure to this substance is still unclear. To answer this question, we housed zebrafish for 10 consecutive days in either 0.50% vol/vol alcohol or system water (0.00% alcohol). Subsequently, each zebrafish was treated with an acute dose of alcohol (0.00%, 0.50%, or 1.00% vol/vol) for 1 hour and their behaviour recorded. Zebrafish were immediately sacrificed after the acute treatment and whole body cortisol levels were quantified. Control zebrafish exhibited an anxiety-induced novelty response demonstrated by preference for the bottom of the tank in the first five minutes of the recording session. Exposure to an intermediate concentration of alcohol (0.50%)

completely abolished this initial preference and decreased cortisol levels reflecting anxiolytic properties of this substance. Alcohol at the highest concentration (1.00%) significantly increased the amount of time spent at the bottom of the tank and increased cortisol, suggesting anxiogenic properties at this highest dose, an effect that was significantly attenuated by chronic alcohol pre-exposure. Overall, the findings here provide face validity for research on the effects of alcohol in zebrafish. The effects appear to manifest in the form of anxiety-like behaviour and hormonal adaptation. The results support the idea that the zebrafish may be a suitable animal model for alcohol related research and behavioural endocrinology.

1-E-134 Co-localization of Somatostatin Receptor Subtype 5 (sst5) with the Receptor-Targeting Protein PIST in the Rat Basal Forebrain

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Somatostatin (SOM) is a neuropeptide whose numerous physiological and neuro-modulatory functions are mediated through a family of G Protein-coupled receptors (GPCRs), designated sst1-5. SOM receptors carry PDZ-binding motifs that regulate dynamic interactions between the receptors and various scaffolding and accessory proteins that also contain PDZ domains. For example, the Protein Interacting Specifically with Tc10 (abbreviated PIST) is a Golgi-associated PDZ protein implicated in the cell surface targeting of sst5 This study sets out to clarify whether sst5 and PIST are endogenously co-expressed in the same neurons of the rat basal forebrain (BF). Through a stereology-based analysis of sst5/PIST dual immuno-labeled sections, we determined that of the sst5 immuno-positive neurons found in the BF, 46% co-expressed PIST (n=3, Gunderson's CoE = 0.04 - 0.09). Specifically, of the sst5 expressing neurons, 51% within the horizontal diagonal band of Broca, 46% within the Ventral Pallidum and 44% within the Olfactory Tubercle also expressed PIST. However, in contrast to findings in cell lines in vitro, where PIST and sst5 co-localized to the trans-Golgi-network, the sub-cellular distribution of both proteins was more complex in situ Our present observations suggest that within the BF, PIST potentially plays a role in the regulation of the sst5 receptor. However, given that no direct evidence for their specific subcellular co-localization is found, PIST may not be the only PDZ protein involved in modulating sst5 trafficking.

1-E-135 The involvement of Tumor Necrosis Factor alpha in the neuronal response to stress

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Stress is known to influence the nervous and immune systems. Acute stress improves rodent performance on tasks involving working memory, through strengthening of neuronal synaptic transmission mediated by circulating corticosterone. We have previously demonstrated that the immune signalling molecule tumor necrosis factor α (TNFα) regulates synaptic transmission through AMPAR trafficking. In light of evidence for the interaction between stress and immune signalling, we set out to investigate the role of TNFα in the neuronal response to stress. To this end, we subjected animals to a forced swim stress test - a paradigm that has been shown to potentiate synaptic transmission in hippocampal neurons. We found that animals genetically deficient in TNFα failed to potentiate synaptic transmission in response to stress. Moreover, injecting wild-type animals with XPro1595, which antagonizes TNFα signalling, abolished the synaptic potentiation in response to stress. Corticosterone in serum of wild-type and TNFα deficient animals was not different at baseline, and increased in both groups to the same extent immediately following stress. Moreover, in vitro corticosterone application to hippocampal slices from wild-type and TNFα knockout animals showed comparable potentiation of synaptic strength, indicating no deficiency in the molecular response to corticosterone in TNFα knockout neurons. Future experiments are aimed at

comparing the physiological and behavioural responses to stress between wild-type and TNFα deficient animals.

1-E-136 Mechanisms underlying a unique form of neuroendocrine adaptation in osmosensitive supraoptic neurons

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The primary hormonal regulator of osmolality is vasopressin (VP), which is released by the magnocellular neurosecretory cells (MNCs) of the supraoptic nucleus as a function of plasma osmolality. MNCs decrease their volume in response to increases in external osmolality and lack the acute volume regulation seen in many cell types. Decreases in plasma membrane tension transduce changes in osmolality into changes in excitability via a stretch-inactivated cation (SIC) channel. Sustained increases in plasma osmolality, however, cause a marked hypertrophy of the MNCs that is thought to be part of a structural and functional adaptation enabling a prolonged high rate of VP secretion. We demonstrate that hypertrophy occurs in isolated rat MNCs in the absence of other cells. MNCs perfused with a saline solution with an osmolality close to the normal set point in the rat (295 mosmol/kg) and then switched to a hypertonic solution (325 mosmol/kg) rapidly shrunk to approximately 94% of control, but after a 10-20 minute delay started to hypertrophy and achieved a size of approximately 105% of control after about 1 hour. The hypertrophy in MNCs was prevented by preincubation with TTX, a SIC inhibitor (SB366791), BAPTA-AM, or nifedipine, suggesting that the response depends on electrical activity, SIC activation, a rise in intracellular Ca2+, and Ca2+ influx through L-type Ca2+ channels, respectively. This suggests a mechanism that is likely to underlie at least part of the osmotically-induced hypertrophy that has been observed in mammalian MNCs in situ.

1-E-137 Synaptic Plasticity of Excitatory Inputs onto Orexin Neurons after Exposure to a Palatable, Energy-dense Diet

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Orexin neurons of the hypothalamus are known to be stimulated by palatable high-fat food and in turn promote further food intake. However, the cellular mechanisms by which high-fat food activates orexin neurons to induce overeating remain unknown Glutamatergic synaptic inputs modulate the excitability of orexin neurons. Therefore, we tested the hypothesis that these synapses undergo plasticity after exposure to a high-fat diet. Whole-cell patch clamp recordings of orexin neurons were performed using acute hypothalamic slices from male Sprague Dawley rats. Rats were fed with standard chow or Western diet (WD) for 7 days. We studied pharmacologically isolated miniature excitatory postsynaptic currents (mEPSCs) and evoked EPSCs We found that the amplitude of mEPSCs in orexin neurons was significantly increased by approximately 50% in WD rats suggesting a postsynaptic potentiation. There was also significantly increased maximal evoked EPSC amplitude in the WD condition. In contrast, the frequency of mEPSCs was unchanged, indicating no change in synaptic contacts or release probability. Despite this, we found that the paired-pulse ratio in WD was significantly higher, suggesting that transmission at these synapses may be more sustainable during repeated activation. This may be explained by altered calcium dynamics at presynaptic terminals In summary, WD induces potentiation of excitatory transmission that may increase the excitability of orexin neurons. Since our rats are not yet obese, this potentiation may be an early change to promote overeating and weight gain.

1-E-138 Warming activates orexin neurons by facilitating excitatory transmission

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Orexin neurons regulate energy balance, wakefulness and thermogenesis. Previously we showed that warming has excitatory and inhibitory effects, whose balance determines the activity of orexin neurons. While the inhibitory effect is mediated by KATP channels, the mechanism for the excitatory effect is unknown. Whole cell patch clamp recording in acute rat brain slices revealed that warming increased the frequency of spontaneous and miniature excitatory postsynaptic currents (sEPSCs and mEPSCs), suggesting enhanced presynaptic glutamate release. Warming also increased mEPSC amplitude, implying augmented postsynaptic sensitivity. These synaptic effects were not blocked by the KATP channel inhibitor glibenclamide, suggesting a mechanism.distinct from that of the inhibitory effect. As transient receptor potential vanilloid (TRPV) channels are heat sensitive, we tested their involvement in the synaptic effect. TRPV1 channel inhibitor AMG9810 blocked the increase in sEPSCs but not mEPSCs, suggesting that warming activates presynapticTRPV1 channels, increasing firing activity. Uncoupling protein 2 (UCP2) is expressed by synaptic terminals impinging on orexin neurons and may elevate local temperature at the synapse. Thus, we tested the effect of genipin, the UCP2 inhibitor, on synaptic activity. We found that genipin did not affect basal mEPSCs, but blocked the increase in mEPSC amplitude by warming. Thus, UCP2 does not influence basal synaptic activity. Overall, warming activates presynapticTRPV1 channels to alter synaptic activity within the neuronal circuitry for energy balance.

F – Cognition and Behaviour

1-F-139 Inhibiting hippocampal neurogenesis promotes memory persistence in infant mice

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Infantile amnesia refers to the inability of adults to remember specific episodes from the first few years of their lives. Most theories of infantile amnesia focus on the idea that forming stable episodic-like memories requires language and a sense of self - characteristics that human infants lack. However, given the fact that non-human animals also demonstrate high rates of infantile forgetting, human-centric theories of infantile amnesia are incomplete. The integration of new neurons into the hippocampus remodels existing neural circuits, which and likely degrades information stored within those circuits. As such, the high levels of neurogenesis in infancy might be causally related to the high rates forgetting displayed by infant animals. The current research had two goals. First, to characterize infantile forgetting in young mice in the Morris Water Maze (MWM) task. Second, to determine whether inhibiting hippocampal neurogenesis in infant mice results in greater memory persistence. To accomplish goal two, we a genetic approach (nestin-tk mice) to ablate neural progenitor cells in infant mice. We found that infant mice (P15-20) can form a spatial memory that lasts 24 h, but that this memory does not persist, and is less accurate than that of older (P25-50) mice. We also found that inhibiting hippocampal neurogenesis in infant nestin-tk mice attenuates infantile forgetting in the MWM, thereby suggesting a causal role for neurogenesis in infantile amnesia.

1-F-140 The Use of CDP-Choline to Modulate Cognitive Processes and Brain State Arousal Implicated in Schizophrenia: A Pilot Study in Healthy Volunteers

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Nicotine-enhanced cognition has been demonstrated with respect to higher order cognitive processes involving attentional, mnemonic, and executive functions. As observed in electroencephalography (EEG) studies, activation of nicotinic acetylcholine receptors (nAChRs),

specifically the low affinity α7 receptor, modulates arousal and information processing during cognitive tasks. Elevated smoking rates seen in schizophrenia (SZ) may be an attempt to correct underlying cognitive deficits, believed to be caused in part by deficient nAChRs. With no effective treatment, a nAChR agonist, 5´-cytidine diphosphate choline (CDP-choline), has been considered as a potential option due to its ability to dose-dependently active α7 receptors. This double-blind, placebo controlled study sought to examine acute dose effects of CDP-choline (0 mg, 500 mg, 1000 mg) on cognitive task performance and resting-state EEG in a healthy surrogate population (N=24) of low, medium, and high performers, expecting the high (vs. low) dose to improve cognition and increase arousal in low performers. Seven CogState tasks and an eyes closed EEG were administered. The analyses revealed an increase in performance among low performers and a decrease among high performers in six of the tasks. EEG analyses revealed a decrease in delta waves and an increase in alpha waves with the 1000 mg dose. These findings confirm CDP-choline's dose-dependent effects and support the use of baseline-dependency in novel drug trials.

1-F-141 Analysis of neuroimaging indicators of functional integrity in the MTL in Temporal Lobe Epilepsy

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Many studies have attempted to identify predictors of postsurgical memory decline due to temporal lobectomy for treatment of temporal lobe epilepsy (TLE) and hippocampal (HC) volume, HC fMRI activations and pre-surgical memory performance have all been shown to correlate with degree of post-operative change. The current study examined the relationship between HC volumes and HC activations with standard clinical measures of memory in a pre-surgical TLE population and identified activation as an intervening variable between volume and memory. Patients performed a novel scene encoding task and the resulting activations within the hippocampus were transformed into asymmetry ratios (AR), (LeftHC-RightHC)/(LeftHC RightHC). HC volumes were measured using a novel multi-atlas technique and were also transformed into ARs using the above formula. Patients were administered standard neuropsychological tests of memory. Performance on memory tests were translated into ARs using (verbal-nonverbal)/(verbal nonverbal). Pairwise correlations between each of the ARs were conducted and a Goodman test was used to assess the significance of activation ARs serving as an intervening variable between volume and memory. We tested the indirect path of volume on memory through activation and found a significant effect. Therefore, while volume ARs, a measure of structural integrity, may represent the necessary substrate for a given brain function, it is the efficiency of activation in that tissue that was a better indication of memory performance attributable to the affected MTL.

1-F-142 Parallel processing streams support dynamic contextual representations in CA1

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The hippocampus plays a key role in the acquisition of new memories for places and events. In rodents, the hippocampus is believed to provide a spatial framework within which items and events can be integrated to form a coherent representation of the animal's experience Sensory information arrives in the hippocampus through two parallel processing streams: place-related information from medial entorhinal cortex (MEC) and object-related information from lateral entorhinal cortex (LEC). Area CA1, the most downstream hippocampal subregion, is unique in that MEC and LEC project to separate neuronal populations. To determine how the convergence of CA3, MEC, and LEC inputs contribute to the processing of object and spatial information in CA1, we studied a transgenic mouse

strain in which synaptic transmission from CA3 is conditionally blocked (CA3-TeTX, Nakashiba et al., Science, 2008) We carried out ensemble recordings in area CA1 of awake behaving CA3-TeTX transgenics and their control littermates as they performed a one-trial contextual learning task. We present physiological data that reflect the anatomical segregation of entorhinal inputs to the hippocampus, and we find that the formation of combined object-place representations requires CA3 input to CA1. Our data support a model where CA3 inputs provide a stable representation of a familiarized context to CA1 while information on new features in the environment arrives through direct inputs from MEC and LEC, and is rapidly integrated to form a conjunctive representation of the animal's present experience.

1-F-143 Inter-hemifield binding of letters into words in ventral occipitotemporal cortex

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We used fMRI adaptation to study the representation of words in ventral occipitotemporal cortex (vOT). Using words split in half at fixation, we identified regions of vOT that represent either whole words or word parts (hemifield-specific halves).We measured fMRI responses to successively presented words that either repeated (all letters repeated), changed in full (all letters changed), or changed in part (half of a word repeated in the left or right visual field and the other half changed). We observed decreased fMRI responses (adaptation) to whole-word repetitions in bilateral posterior vOT and the 'visual word form area' (VWFA) in left vOT. Unlike posterior vOT, which adapted to half-word repetitions, the VWFA only adapted to whole-word repetitions. A second experiment found that all of these areas--and also a putative VWFA homologue in the right hemisphere--showed maximal sensitivity to centrally presented words and a contralateral whole-word position bias, but did not exhibit the same pattern of adaptation to words as its left vOT counterpart. Additional experiments identified portions of posterior OT that showed maximal half-word adaptation as an area involved in the visual processing of faces. In contrast to this bilateral face-selective area in posterior OT, the VWFA in left OT showed greater fMRI responses to words as compared to non-words of similar size and complexity. We conclude that bilateral posterior vOT represents hemifield-specific partial word forms, whereas the VWFA in left vOT represents words as whole units.

1-F-144 D-KEFS Color-Word Interference Test as a potential measure of cognitive fatigue in multiple sclerosis: A pilot study

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Background: Fatigue is a hallmark symptom of multiple sclerosis (MS). Cognitive fatigue (CF) can be defined as an inability to sustain task performance throughout a continuous cognitive task. Both within-task and across-session CF can be examined. Effectiveness of the D-KEFS Color-Word Interference Test (CWI) at detecting CF was examined, as was the relationship between objective and subjective fatigue. Methods: As part of a larger study on cognition, 16 individuals with early relapsing-remitting MS completed a neuropsychological battery with the CWI administered both pre- and post- testing. Results: Within-task CF was noted at both administrations on Color and Inhibition tasks, with evidence of CF noted on Inhibition-Switch task at the second administration. Performance on each task differed between the two administrations with the Color and Word tasks remaining relatively stable, while the Inhibition and Inhibition-Switch tasks improved over time (i.e no evidence of across-session CF). No significant difference was found in the frequency or type of error made between the two administrations. The relationship between subjective and objective fatigue varied based on the methodology used. Conclusions: The CWI is a sensitive measure of within-task CF in MS; particularly the Color and Inhibition tasks. There

was no evidence of across-session CF; rather, practice effects were apparent. Findings with the CWI are consistent with past literature suggesting that within-task performance differences provide a valid representation of CF.

1-F-145 Open-field Turning Behaviour Elicited by Pharmacogenetic Activation or Inhibition of RMTg GABA Neurons in GAD2-CRE mice

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RMTg GABA neurons powerfully inhibit VTA and substantia nigra DA neurons important for reward and turning. Unilateral lesions of the RMTg produce contraversive turns (Bourdy et al., 2012) while electrical stimulation elicits ipsiversive turns. To investigate how these GABA neurons control turning, GAD2-Cre mice received unilateral RMTg AAV infusions of excitatory HM3D or inhibitory HM4D receptors, commonly called DREADDs. Unilateral AAV-infusion alone produced contraversive turns in several mice, consistent with RMTg inhibition. HM4D-transfected mice produced even more contraversive turns in response to 2 mg/kg CNO. Conversely, HM3D-transfected mice had fewer contraversive and more ipsiversive turns after CNO. Transfected neurons were identified through AAV-mCherry fluorescence and confirmed with RMTg markers including nociceptin, GAD67, mu-opiate receptor and amphetamine-induced Fos expression. We are currently investigating the effects of morphine and amphetamine on CNO-induced turning, to assess the relations between opiate receptors, dopamine neurons, and RMTg GABA functions.

1-F-146 Neural activity build-up during decision-making is not attributable to evidence accumulation but to a growing urge to act

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Many studies, including extracellular recordings in monkeys and neuroimaging in humans, have reported that during decision-making tasks, neural activity builds-up at a rate related to the strength of sensory evidence. Almost without exception, this is interpreted as the gradual accumulation of evidence to a decision threshold, often called the "bounded accumulation" model. However, an alternative explanation exists: that the build-up is due to an urgency signal that gradually increases the gain of sensory information as time is passing. In most conditions previously tested, sensory information is constant over time, which renders these models mathematically identical and therefore indistinguishable. However, recent studies aimed at distinguishing these models (by presenting information that changes over time) strongly support the latter, "urgency-gating" model. Here, we summarize these studies and present the mathematical foundation for why the urgency-gating model performs better than the bounded accumulation model. First, it discounts redundant information, emphasizing novelty. Second, it maximizes what animals care about most - their reward rate. In summary, despite the widespread acceptance of the bounded accumulation model as the explanation for a large variety of behavioral and neurophysiological results on decision-making, we suggest that nearly all of those results are better explained with the urgency-gating model. Support: CIHR (MOP-102662), CFI, FRSQ, and EJLB Foundation, FYSSEN and GRSNC fellowships to DT.

1-F-147 The Effect of Post-training Cocaine Administration on Acquisition of the Win-Stay Task in Cocaine Sensitized Rats

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Rationale - It has been proposed that drugs of abuse reinforce behavior partly, or wholly, because they enhance memory consolidation. Cocaine is a drug with high abuse potential, but evidence that it can enhance memory consolidation has been difficult to obtain in appetitive tasks because of its side effects. Objectives - To determine whether cocaine sensitization can reduce the side effects of cocaine and thus allow observation of an action of

cocaine on memory consolidation. Methods - Male Sprague-Dawley rats were pre-exposed to cocaine (30 mg/kg/day, x 5 days followed by 7 days drug-free) before testing acquisition of an appetitive Win-Stay task reinforced by sucrose in an 8-arm radial maze. Rats were injected with cocaine (0, 2.5, 7.5 and 20 mg/kg, IP) immediately following training. Results - During maze training, no differences in performance were observed, and rate of acquisition was not affected by cocaine dosage. Conclusion - Sensitization can reduce the side effects of cocaine, but it does not appear to enhance the action of this drug on memory consolidation. The implication of these data for the memory consolidation hypothesis of drugs of abuse is discussed. Keywords: Cocaine, Memory Consolidation, Reinforcement, Win-Stay, Sensitization, Rat

1-F-148 Decision-making is influenced by a context-dependent urgency signal: model and experimental data

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Many models of decision-making propose an accumulation of sensory information to a decision threshold. These models can explain data from human and nonhuman primate studies during tasks in which the decision-relevant information is held constant over the course of a trial. However, they don't address the more ecologically valid scenarios in which evidence varies over time. An alternative model has been proposed, based on an attractor network whose dynamics are modulated by a context-dependent "urgency" signal. The growth of the urgency signal makes the model increasingly sensitive to perceptual evidence over time, thus implementing an experimentally observed dropping criterion effect. This makes a strong prediction: that during the classic random-dot motion discrimination task, the response to brief motion pulses will depend on task context. Here, we present experimental data supporting this prediction by demonstrating that, on identical trials, response time and the effects of motion pulses strongly depend on the mixture of trials with which human subjects are presented. These results run counter to predictions of traditional bounded accumulation models and are best accounted for by an urgency signal that modulates the dynamics of an attractor network. Support: CIHR (MOP-102662), CFI, FRSQ, and EJLB Foundation, FYSSEN and GRSNC fellowships to DT, European Community FP7/2007-2013 Grant 270108.;

1-F-149 Effects of acute cocaine on rat inhibitory control tested with the countermanding paradigm

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The countermanding task measures inhibitory control by examining a subject's ability to withhold a response to a go stimulus when a stop signal is presented sporadically (Logan & Cowan, 1984). In rats, acute administration of amphetamine resulted in go response speeding and changes in stopping ability dependent on baseline performance; the faster a rat stopped, the more impaired (slower) it was following drug administration (Eagle & Robbins, 2003; Feola et al., 2000). We hypothesized that acute cocaine would produce changes in task performance that were similarly dependent on individual baseline behaviour. Male Wistar rats were trained to respond to a visual stimulus (go signal) by pressing a lever below an illuminated light for food reward, but to countermand the lever press (25% of trials) subsequent to an auditory tone (stop signal) presented after a variable delay. Rats were randomly administered cocaine (0, 0.1, 1 and 3 mg/kg; i.p.) prior to test sessions. Cocaine (1 and 3 mg/kg) significantly slowed go responses, while affecting stopping in a baseline-dependent manner. This inhibitory control impairment was in part related to the magnitude of slowing in go responses, thus reflecting general task performance impairment. These results show that, despite impairing stopping similarly, cocaine and amphetamine differentially impact go responses,

providing evidence for independent effects on neural go and stop processes. (Funded by NSERC).

1-F-150 Using CDP-Choline to Modulate Sensory Memory Processes Implicated in Schizophrenia: A Pilot Study in Healthy Volunteers

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Cognitive deficits have been proposed to be the core symptom of schizophrenia (Sz), yet antipsychotic medications do not alleviate these symptoms. As acetylcholine is known to play an important part in cognition, namely in sensory, attentional, mnemonic and execute functions, and there is dysregulation of the acetylcholine receptor (nAChR) system in Sz which may cause these deficits, cholinergic agonists have been proposed as a novel drug treatment for this disorder. This study examined the effects of 5´-cytidine diphosphate choline (CDP-choline), a selective α7 nicotinic acetylcholine receptor (nAChR) agonist, on sensory memory processes. Mismatch negativity (MMN), an event-related potential (ERP), is an index of auditory sensory memory, which has been found to be consistently diminished in Sz. MMN is a biomarker of Sz and has been proposed as a potential measure to assess efficacy of novel medications for cognitive improvement in Sz. In 24 healthy male controls, we examined the dose-response effects of CDP-choline on sensory memory-indexed MMN in 3 separate sessions (0mg, 500mg, 1000mg). As drug effects have been found to be baseline-dependant, we assessed MMN in low, medium and high individuals. Results show that in low MMN individuals, both doses of CPD-choline were shown to improve sensory memory. In high MMN individuals, CPD-choline was found to diminish MMN. These results demonstrate that CPD-choline can improve sensory memory in individuals with poor cognitive function and supports the adjunctive use of cholinergic agonists to alleviate cognitive impairment in Sz.

1-F-151 The effect of male pheromones on the estrous cycle of female rats as seen in wheel running patterns

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A distinct pattern of running has been seen in female rats across the 4-day estrous cycle. Running during the estrus phase is elevated by over 100% (Eckel, 2000). In rodents, the female estrous cycle can be affected by male pheromones. Male pheromones can increase synchronous estrus among a group of female mice, known as the Whitten Effect (Whitten, 1956). Conversely, the absence of males can suppress or disrupt the estrous cycle in female mice, coined the Lee-Boot effect (Lee & Boot, 1956). This study explored the effects of male pheromones on wheel running in female rats to see if these two effects would be evident. 32 female rats were housed in a unisex colony room, either individually or in pairs, and were given wheel access. Another 12 females were pair housed or individually housed with males in the room and were given wheel access. In both cases, half of the females were pair housed to test the effects of close proximity. Wheel turns, food intake and body weight were measured daily. Preliminary analysis suggests that female estrous cycle synchrony and regularity are influenced by the presence or absence of males. Both pair and individually housed females, when housed with males, demonstrate enhanced estrous synchrony and have a more regular cycle, as seen in running patterns. Unisex housed females were less regular in their cycle, as demonstrated by running levels and showed almost no synchrony.

1-F-152 Representational differences influencing the facing-the-viewer bias in the perception of ambiguous figures

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Point-light walkers (PLWs) and stick figures generally do not contain information about their in-

depth orientation, yet observers prefer to report a facing-the-viewer (FTV) interpretation (Vanrie et al., 2004). It is not clear why this is the case While silhouette figures are equally depth-cue deprived, results show that the well-known Kayahara silhouette does not elicit the same facing bias as PLWs do (Troje & McAdam, 2010) If stick figures are subject to a FTV bias but the silhouette is not, then the cause for the facing bias must rest in one of the several differences between the two stimuli. In order to isolate the critical features, we measured FTV bias while systematically manipulating a number of attributes that differ between the two stimuli: gender, posture, dynamic vs. static presentation, display type (sticks vs. outline) We asked 10 observers to continuously report rotation directions (clockwise/counter clockwise) of all displays and measured FTV bias as the proportion of reversals from the 'away' to 'towards' interpretation Results indicated that most stick figures elicited a facing bias that was not present in silhouettes. Interestingly, the static, standing stick figure--which has little variation in depth along the anterior-posterior direction--elicited no bias. These findings provide a compelling tool for explaining the FTV bias in terms of differences between silhouettes, the standing SF and other variants. Our findings strongly suggest that the facing bias is driven by local stimulus features. Interpretations are discussed.

1-F-153 The Use of CDP-Choline to Modulate Attentional Processing Implicated in Schizophrenia: A Pilot Study in Healthy Volunteers

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Cognitive deficits are prominent in schizophrenia (SZ) patients, impact their ability to integrate into society, and are not alleviated by antipsychotics. As 60-80% of SZ patients are smokers, it's hypothesized that nicotine is used due to its cognitive enhancing properties in the realm of attention. CDP-choline, a selective alpha 7 nicotinic receptor agonist, mimics nicotinic activity in neural systems underlying attention. CDP-choline has been shown beneficial for cognitive deficits in neurological disorders and in the elderly. Objective: To examine the acute differential effects of 500 & 1000 mg of CDP-choline on attentional processing indexed by the P300 event related potentials (ERPs), which are deficient in SZ. P300 nicotine related improvements have been observed in SZ patients and healthy subjects therefore we expect CDP-choline (vs. placebo) to enhance early attentional processes where greater enhancement is expected with the 1000 mg dose. Methods: Employing an auditory odd-ball paradigm, CDP-choline's effects on N1, P3a and P3b ERPs were examined in 24 healthy, non-smoking males during three testing sessions. Results: Increased N1, P3a and P3b amplitudes were observed in individuals with low baseline amplitudes under the 500 mg dose (vs. placebo). Additionally, in individuals with high baseline amplitudes this dose expressed a decrease in N1, P3a and P3b amplitudes. Conclusion: Our findings are in accordance with previous nicotinic results, and suggest that the 500 mg dose of CDP-choline is optimal and beneficial for impairments in early attentional processing.

1-F-154 Enhanced association-memory due to imagery, but without enhanced engagement of the hippocampus

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The hippocampus (HPC) has been identified as being important for learning associations. However, several manipulations are able to lead to better association-memory, without enhanced HPC engagement, such as compound words and unitization. Another process that could lead to enhanced association-memory via a non-HPC mechanism may be imagery. Pairs of high-imageability words (e.g., BIKE-STOVE) are remembered better than pairs of low-imageability words (e.g., CLAIM-RATIO). Here we asked if

imagery enhanced association-memory by engaging the HPC more, or if this memory enhancement was produced independent of the HPC. In an event-related fMRI task, participants studied word pairs and were tested with cued recall. HPC activation was equivalent for high- and low-imageability pairs (i.e., no main effect of imageability). As expected, we observed main effect of memory on HPC activity (subsequent memory effect [SME]). Importantly, as more high-imageability pairs were recalled (better cued recall accuracy), recalled high-imageability pairs were associated with significantly less HPC activity than low-imageability pairs. We additionally found a SME specific to high-imageability pairs in the anterior cingulate cortex, suggesting that additional brain regions are boosting association-memory beyond the contribution of the HPC. Importantly, prior results demonstrated that imageability enhances association-memory, rather than memory for the target, independent of its association. Our results demonstrate that imagery can enhance association learning through brain regions other than the HPC.

1-F-155 Gestational stress and affective changes in rat dams

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Postnatal depression is a significant and serious illness with a reported incidence of approximately 14%, while a further 30% of women experience adjustment disorder and anxiety following childbirth. Gestational manipulations produce well documented alterations in the progeny in terms of physiology and behaviour. One relevant factor known to programme endocrine and behavioural responses in the offspring of experimental animals is chronic, prenatal stress. Aim: To investigate the possible factors that might be responsible for the change in maternal behaviour that occurs following Gestational Stress (GS) exposure. Methods: Porsolt Test :On days 17-20 of gestation or days 4-5 post-delivery, selected dams underwent the Porsolt forced swim challenge, a model of depression. The test is done over 2 days, and consists of being placed in a water tank (water at 22 C) for 10 minutes on exposure day (day 1) and 5 minutes on experiment day (day 2). Elevated Plus Maze: On days 17-20 of gestation or days 4-5 post-delivery, selected dams underwent Elevated Plus Maze testing for anxiety. Results: 1. Gestational Stress & Depression Immobility times in the Porsolt test were increased in stressed dams compared to controls prior to their giving birth and remained increased over postnatal days 4/5. 2. Gestational Stress & Anxiety Time spent in both the open and closed arms of the EPM were highly variable for both gestationally-stressed dams and non-stressed controls. Conclusion: Gestational stress induces depressive-like, but not anxiety-like, behaviour in rat dams.

1-F-156 Cognitive effects of lesions in the anterior pedunculopontine tegmentum in rats

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The pedunculopontine tegmentum (PPT) is part of the mesopontine cholinergic system in rats. Posterior regions (pPPT) receive sensory input and send connections to dopaminergic (DA) cells of the ventral tegmental area (VTA). Anterior regions (aPPT) receive input from basal ganglia/forebrain and send connections to DA neurons of the substantia nigra (SN). These differences in connectivity suggest functional dissociation between pPPT and aPPT. In a recent study, pPPT-lesioned rats had difficulty associating lever pressing with reward. Subjects performed similar to controls if association learned prior to surgery, indicating pPPT is important for formation of reward association but not thereafter. Conversely, aPPT-lesioned rats showed less obvious deficits. Since aPPT connectivity with SNc neurons and dorsal striatal circuitry is analogous to pPPT connectivity with ventral striatal circuitry, we hypothesize that aPPT should be important for dorsal striatal associative learning. Additionally, aPPT-lesioned rats may show sensory filtering deficits, since they have shown to be modulated by

DAergic activity. Subjects underwent either sham (saline) or lesion (ibotenate) bilateral microinjections into aPPT and were subsequently tested in a cued-water maze and for habituation and prepulse inhibition (PPI) of acoustic startle. Lesioned rats showed normal PPI but no short-term habituation. Preliminary water maze results suggest lesioned rats showed trends towards slower learning. These data suggest aPPT may play a role in short-term habituation and dorsal striatal associative learning.

1-F-157 Behavioural Consequences of NMDA Receptor Hypofunction During Critical Stages of Development

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The current genetic and environmental risk factors for schizophrenia are largely neurodevelopmental. Despite the developmental nature of these insults, symptoms of the disease do not emerge until adulthood. Susceptibility genes for schizophrenia converge on glutamatergic transmission and suggest a state of NMDA receptor (NMDAR) hypofunction is present in the schizophrenic brain. If impaired NMDAR function is a feature of the disease, we hypothesize that the behavioural consequences of NMDAR hypofunction will only be fully evident in adulthood. To test this hypothesis, we used a genetic mouse model of NMDAR hypofunction, NR1 knockdown mice (NR1-KD). We assessed behavioural consequences of NMDAR deficiency through critical stages of development to trace the onset and progression of schizophrenia-related phenotypes. Sociability, working memory, stereotypic behaviour, and executive function were assessed in juvenile (3wk), post-adolescent (6wk), and adult (12wk) NR1-KD mice. In these domains, juvenile NR1-KD mice were either behaviourally normal or displayed a milder phenotype than adults. Specifically, deficits in sociability and working memory were only observed in adult mutant mice; however, repetitive behaviour and impaired executive function were detected in juvenile mice and further deteriorated in adulthood. Our findings support the hypothesis that the behavioural consequences of impaired NMDAR function are most evident in adulthood. This may indicate different roles for NMDARs in the developing and mature brain.

1-F-158 Mice deficient for BK potassium channels show sensory gating deficits and impaired spatial memory

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Habituation and prepulse inhibition (PPI) of startle are measures of sensory gating. Although the pathways are well described, the cellular/molecular mechanisms underlying sensory gating are not yet well known. Deficits in sensory gating have also been strongly associated with other cognitive deficits. Mutations in C. elegans and Drosophila have indicated that functional large conductance calcium and voltage activated potassium channel (BK channel) are required for short-term habituation (STH), and these channels have been suggested to directly influence synaptic transmission. We tested mice with and without a genetic disruption of the BK channel for STH of startle as well as for PPI and distal spatial acquisition. WT-animals habituated to 69% of their initial startle response, while there was no significant STH in KO-animals. PPI was also significantly attenuated in KO-mice Heterozygous littermates were intermediate in both tasks. Acquisition of a spatial memory task was impaired in KO mice compared to WT and HETs, but was retained once acquired with no significant difference in reference memory between KO and WT animals. The data suggest that activation of BK potassium channels in the brainstem is crucial for STH of startle, confirming invertebrate findings. Additionally, BK channels seem to play an important role in PPI, indicating that fine tuning of synaptic efficacy by BK channels may be more generally involved in sensory gating processes. BK channels seem to play a role in cognition in terms of spatial acquisition. .

1-F-159 Conditioned reinforcement in the mouse: effects of enhanced dopaminergic activity induced by methylphenidate and amphetamine

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Reward associated stimuli acquire incentive properties making them wanted in their own right as conditioned reinforcers (CR). Incentive salience attribution to stimuli is partially dopamine (DA) dependent, demonstrated in tests of operant responding for CRs. While rats are commonly used in the CR paradigm, little attention is paid to mice which offer a wide range of genetic manipulations to examine mechanisms of incentive learning. These experiments assessed whether 1) mice can learn a stimulus-reward association, 2) that stimulus functions as a CR, and 3) responding is altered by enhancing DA activity. Separate groups of water-restricted C57Bl/6 or CD1 mice received 30 pairings of a conditioned stimulus (CS; light+noise) with 0.01 ml 0.2% saccharin in 14 daily 40 min sessions. Mice were then allowed access to a lever delivering the CS (now a CR). Responding for the CR was assessed following i.p. administration of the DA reuptake blocker methylphenidate (MPH; 0, 3.5, 5 mg/kg), or the DA releaser amphetamine (AMPH; 0, 0.1, 0.3, 0.5, 1, 1.5 mg/kg). All mice approached the saccharin magazine during CS presentations and later selectively lever pressed for the CR. MPH only increased responding for the CR in CD1 mice, while AMPH had no obvious response enhancing effect and instead reduced responding at higher doses. These results show that mice learn the incentive value of a CS and work to obtain it as a CR. Therefore, mice can be used to examine mechanisms of incentive learning; however, the response enhancing effects of DA agonists may be more subtle than what is seen in rats.

1-F-160 Effects of chronic stress and alcohol exposure during protracted withdrawal

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Research has established a relationship between stress exposure and dysregulation of reward-systems, which has been linked to addictive and anxiety-like behaviours. Previous studies have also demonstrated alteration of reward- and stress-related neurocircuitry following chronic stress or drug exposure. Thus far studies have largely focused on the acute effects of stress, however drug relapse often occurs during protracted withdrawal - a period not characterized by overt physical symptoms. Male Wistar rats (N = 96) received either a 6-week chronic unpredictable stress regimen, ethanol liquid diet (LD), or both; a naive control was also included. Following a two-week period of abstinence subjects were tested on the elevated plus maze, and for ethanol-conditioned place preference (CPP). The results replicate previous findings and extend the research by examining the interaction between prior chronic stress and ethanol exposure on the dose-response profile in CPP, and have implications for understanding protracted relapse risk.

1-F-161 Noise correlations contribute to the encoding of attended locations by neuronal populations in the macaque dorsolateral prefrontal cortex

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Interactions between neurons in the primate dorsolateral prefrontal cortex (dlPFC) are thought to play an important role in visual attention. However, such interactions have been poorly investigated. We examined neuronal interactions in dlPFC in a macaque monkey during a task that required allocating and sustaining attention to one of two moving random dot patterns (RDPs). The animal had to select the target RDP based on a color cue according to an ordinal scale (turquoise>red>blue>green>pink>grey), sustain

attention to it, and indicate a change in motion direction while ignoring similar changes in the other RDP. We recorded the responses of 607 neurons with a 96-electrode microarray during two task epochs: a) color cue presentation, and b) sustained attention period. The firing rate of 168 neurons was significantly modulated by target location (101 were selective for ipsilateral and 68 for contralateral targets). We computed noise correlations between neurons as a function of target location and distance between stimuli on the scale. Noise correlations were significantly higher than predicted by chance during both epochs for all populations. We compared the performance of a binary linear classifier (Support Vector Machine (SVM)) at predicting the target location on the real data and on the same data but with shuffled trials, thus destroying the simultaneity and the correlation structure. Removing correlations led to a decrease in the SVM classification performance. Thus, noise correlations significantly and positively contribute to encoding attended targets in the dlPFC.

1-F-162 Ensemble dynamics in the responses of mitral cells to odors

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Immediate-early genes such as Arc, which is critical for behavioral expression of learning and enduring synaptic plasticity, have been used in a number of cortical structures to determine the ensemble activity associated with information processing. Here we apply this technique to examine the pattern of Arc expression in mitral cells of the olfactory bulb (OB) in response to odor. Preliminary results suggest that the same mitral cell is more likely to transcribe Arc following repeated exposure to the same odor (in this case, peppermint) relative to mitral cells of animals exposed to 2 different odors (peppermint and amyl acetate), suggesting that the mitral cell response to odors is input-specific, and that Arc can be used as a specific marker of activity in these cells. We are currently investigating the extent to which the mitral cell response to odors can be modified by conditioning. Pairing a novel odor with tactile stimulation in rat pups has been shown to produce a robust and long-lasting preference for the paired odor. Rat pups were separated into four groups during training such that some pups were exposed to peppermint while receiving tactile stimulation; others received this with the left olfactory bulb plugged, while others only received yoked olfactory experience. Caged controls received neither olfactory nor tactile stimulation. Twenty-four hours after training, some pups completed an odor preference test, others were re-exposed to the peppermint-odor or the control odor, amyl acetate, in order to examine Arc expression in mitral cells following these odors

1-F-163 Reduction of Synapsin II in the medial prefrontal cortex of Sprague-Dawley rats results in schizophrenic-like cognitive abnormalities as apparent in the 5-choice serial reaction time task

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A reduction in synapsin II (SynII) expression in the medial prefrontal cortex (mPFC) of adult male Sprague-Dawley rats has been shown to result in behaviors that are analogous to the negative and/or positive symptoms of schizophrenia. Knockdown of SynII can be accomplished experimentally via continuous infusion of anti-sense deoxyoligonucleotide (ADON) sequences, as detailed by Dyck et al. (2001, 130:250-9) This study examined the effect of SynII knockdown in the mPFC on 5-choice serial reaction time task (5-CSRTT) performance. The 5-CSRTT is used to study the attentional process of subjects; where in, the accuracy of response is an indicator of attentional capacity. Other behaviors (omissions, premature responses, etc.) can also be measured to characterize abnormalities of motivation, impulse control, and other executive functions. Following initial 5-CSRTT training, rats underwent stereotaxic surgery to achieve delivery of ADONs via implanted cannulae and osmotic pumps. Upon recovery, rats were again subject to testing in the 5-CSRTT. The

SynII ADON treated subjects were characterized by a decrease in correct-response percentage as well as an increase in omissive responses when compared to control groups. These behavioral differences were also accompanied by increased latencies of response, while having no observable deficits in number of premature responses, total nose-poke responses or perseverative responding. Thus, SynII knockdown in the mPFC resulted in reduced 5-CSRTT performance, which can likely be attributed to deficits in cognitive ability.

1-F-164 Biological motion perception in the elderly

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In this study we tested participants from two different age groups on eight tests that are designed to test different aspects of biological motion, such as the direction of motion perception, ability to detect a point-light walker in noise, sensitivity to local biological motion invariants, ability to extract structure from motion, action recognition, gender discrimination, and two versions of an identity test: naming and recognition of stick figures Results for 26 older adults (mean 64 y) are compared to a group of 30 young adults (mean 23 y) from Saunders and Troje (2011). Consistent with Bennett et al (2006), older adults needed more coherent dots to tell direction of motion. Consistent with Pilz et al (2010), older adults could not tolerate as many noise dots as young, implicating a problem with figure-ground segregation. Scrambled walkers were used to test sensitivity to local biological motion invariants and results indicate that older adults have lower sensitivity. Finally, the recognition test was administered twice with an intermittent naming test. Older adults did not differ from young on block one but had a significant decrease in performance on block two. This indicates that older adults are generally capable of identifying stick figures when tested without interruptions Older adults did not differ from young on the other tests, indicating that the ability to extract structure from motion, action recognition, gender discrimination, and the ability to identify walkers do not decay with age.

1-F-165 Motor and cognitive abilities of the transgenic LRRK2 Rat Model of Parkinson Disease

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Genetic mutations in the leucine-rich-repeat kinase 2 gene cause late onset, autosomal dominant familial Parkinson's Disease (PD). LRRK2 mediated PD is clinically indistinguishable from idiopathic PD, suggesting similar underlying pathways. As a result, further understanding of the LRRK2 pathophysiology can provide insight into PD etiology and development of disease intervention. Here, we describe the characterization of transgenic BAC rats expressing human LRRK2 bearing the familial PD mutation, R1441G. Due to the progressive nature of PD, these rats are tested for motor and cognitive deficits, reminiscent of Parkinson's disease through developmental stages of 3, 6, 9 and 12 months. Transgenic rats undergo a battery of motor testing, including open field, movement initiation, postural stability and gait stride test. To assess cognitive deficits, rats are tested in the Morris water maze, and for habituation and prepulse inhibition of startle. In addition to behavioural testing, transgenic rats will also undergo high resolution anatomical imaging to identify neurodegeneration over time. We hypothesize that these rats show no deficits at three months of age, but may show initial deficits as early as 6 months of age, and that these deficits will worsen as they further age. Preliminary testing indicates that LRRK2 transgenic rats are not significantly different from their wildtype counterparts at the 3 month stage on either motor or cognitive tests. A first cohort of 6 months old rats is currently being tested.

1-F-166 Spike count correlation variability in visual, presaccadic, and visuopresaccadic neurons of macaque dorsolateral prefrontal cortex during a working memory task

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We examined spike count correlations between neurons in prefrontal area 8A of two Macaca fascicularis during an oculomotor delayed-response task using Utah microelectrode arrays. The task consisted of fixation on a central spot, presentation of a circular sine wave grating at one of 16 locations, extinguishing of the grating and a delay period; finally, the fixation point was extinguished, cuing the animals to saccade to the remembered location. We isolated responses of 191 single units for a total of 1170 neuronal pairs. Neurons were classified as selective (one-way ANOVA, $p<.05$) for visual stimuli (visual, n = 29), future saccade location (presaccade, n = 22), or both (visuopresaccade, n = 78). The proportion of significant positive correlations within all three groups of units were greater than chance during the stimulus, delay, and presaccade epochs ($p<.05$). The proportion of significant negatively correlated presaccadic units was higher than chance during the delay epoch ($p<.05$), and proportions of significant negatively correlated visual units were greater than chance in all three epochs ($p<.05$). Linear classifier (support vector machine) performance was best when decoding stimulus position from firing rates during memory (57%), followed by the stimulus (45%), and the presaccade (32%) epochs. Our results show that visual, presaccadic, and visuopresaccadic units in area 8A exhibit different degrees of correlated firing depending on task demands. Thus different prefrontal neurons may play different roles during working memory maintenance and goal selection.

1-F-167 Content Specificity of the Contralateral Delay Activity

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How might the content held in conscious awareness affect the neural correlates of awareness? Here, we manipulate object category as participants have the sensation of an object moving in and out of awareness. We explored this phenomenon through a bilateral Shape-from-Motion (SFM) display, while recording neural activity using EEG. The SFM display involves a line drawing of an object moving in counter-phase to randomly oriented background lines. During the motion phase, the object can be easily segregated from the background. When the motion stops, the percept persists for a little while in the observer's experience before it fades from conscious awareness. Previous work has shown that the electrophysiological correlate of visual working memory (VWM) - the contralateral delay activity (CDA) - is recruited during this perceptual persistence period suggesting that VWM may play an important role in subjective awareness. Here, we tested whether this electrophysiological component of VWM engagement is sensitive to the content of visual awareness. We find a difference in the presence and amplitude of the CDA between object, animal, and human face stimuli. This effect of object category suggests that the specific content being held in awareness may be stored or maintained differently in VWM.

1-F-168 Crossmodal object recognition: Involvement of the perirhinal and posterior parietal cortices in binding visual and tactile object information

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Object recognition can be enhanced by the ability to process object features from different sensory modalities. We have previously shown that rats rely on interaction between the posterior parietal (PPC) and perirhinal (PRh) cortices to perform a tactile-to-visual spontaneous crossmodal object recognition (CMOR) task. Interestingly, providing rats with a brief simultaneous pre-exposure (PE) to the tactile and visual properties of the sample object enables performance of this task with retention delays that

otherwise prevent successful recognition. In the current study, we assessed the role of PRh and PPC in the formation of multisensory object representations which may be responsible for this enhanced performance. Male Long-Evans rats were tested in the CMOR paradigm with and without PE. Immunohistochemical staining for the immediate early gene c-fos indicated activity in PRh following multimodal PE to objects. Furthermore, transient inactivation of PPC and PRh at different phases of the CMOR and PE/CMOR tasks revealed differential roles for these two structures. Specifically, PPC activity was necessary during the choice phase of the original CMOR task, but not when rats received multimodal PE to the objects; PRh was required at the choice phase in the latter case. Moreover, PRh was required at the sample phase when PE was necessary for task performance, but not when CMOR was possible without PE. These results extend previous findings implicating PRh in object representation and suggest an important role for PRh in associating multisensory object features.

1-F-169 Do human brain areas involved in visuomotor actions show a preference for certain tool orientations?

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Brain regions along the "vision-for-action" dorsal stream have been shown to preferentially activate to graspable over non-graspable objects. Notably, the caudal intraparietal sulcus (cIPS) has been suggested as a region within the dorsal grasping circuit that processes orientation, particularly for tools. What is unclear is whether areas such as cIPS show preferential activation for tools oriented with the handles toward or away from the dominant hand. Right-handed subjects were scanned with a 3 Tesla functional magnetic resonance imaging (fMRI) scanner while passively viewing centrally-presented tools with their handles oriented either towards the left or right. As a control stimulus, we generated non-tools by scrambling the features of our real tools along both ends of their original handle such that the size and orientation were matched. Unlike the tools however, the non-tools lacked clear structural affordances and functionality. Thus, we hypothesized that regions along the "vision-for-action" stream would activate preferentially to left or right oriented tools however would not do so for our non-tools. Indeed, we observed preferential activation in left cIPS for real tools when their handle was oriented toward the subjects' left hand vs. right hand (or to phrase it another way, with the business end in the right vs. left visual field). These results demonstrate that regions such as cIPS not only preferentially respond to graspable stimuli but also show a preference for tool orientation.

1-F-170 Olfactory learning in the rat pup modifies mitral cell layer mRNA expression

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Neonate rats rely on odor cues to identify the dam for food and warmth. Olfactory learning modifies behavioral, neural and metabolic responses to the odor. The 24 h odor preference memory produced by a single training trial is dependent on CREB phosphorylation in mitral cells of the olfactory bulb. This odor preference memory requires transcription during the first 60 minutes after training. We previously showed that there is increased pCREB labelling in the dorsolateral (DL) quadrant of mitral cells in learning pups (odor tactile stimulation) compared to non-learning pups (odor only). In the present study, odor stroking and odor only groups were sacrificed 50 min after training, having confirmed presence or absence of odor memory at 30 min after training The DL quadrant of the mitral cell layer was isolated using a laser microdissection (LMD) microscope. Messenger RNA was analysed by a >20,000 gene microarray. Only sixteen genes differentiated the learning and non-learning mitral cell extracts. Thirteen genes with at least a 1.5- fold difference in expression were analyzed using qPCR. Significant differences in qPCR levels at the same time point were seen in several of the thirteen genes isolated. The genes confirmed as changing with learning are involved in cell neurogenesis and

growth while others have a role in neurite differentiation and vesicle formation and transport. The pattern of results is consistent with the hypothesis that the growth of processes and the insertion of receptors in mitral cells accompany early olfactory learning.

1-F-171 Maternal high fat diet alters anxiety, stress, and inflammatory signaling in the brain of adult rats

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For offspring, maternal obesity and a diet high in saturated fat during pregnancy carry significant risks for health problems that manifest later in life, including the metabolic syndrome and affective disorders. Consumption of a high fat diet increases peripheral inflammation and recent studies show that maternal high fat directly increases inflammation in the hypothalamus of offspring. Yet few studies have examined effects of high fat diet exposure on inflammatory processes in limbic brain areas as a mechanism for anxiety and corticosteroids as modulators of inflammation and stress-mediated behaviour. We hypothesized that inflammatory gene expression in limbic brain areas is associated with increased anxiety and stress as a function of developmental high fat diet exposure. High fat diet-exposed offspring show increased anxiety-like behaviours, decreased basal circulating corticosterone levels and a slower return to baseline following a stressor. High fat diet-exposed offspring also show sex-specific alterations in corticosterone receptor and inflammatory gene expression in the hippocampus and amygdala, brain areas known to regulate anxiety and the response to stress. The data indicate that developmental high fat diet exposure may alter behaviours associated with affective disorders at least in part by inducing long-term changes in inflammatory signaling pathways in limbic brain regions.

1-F-172 Recognizing Famous Individuals: A Deficit in Patients with Capgras Syndrome?

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Capgras Syndrome (CS) is characterized by the mistaken belief that individuals personally familiar to the patient have been replaced by an imposter, or "double." The current experiments tested the hypothesis that patients with CS also have recognition impairments that extend beyond those individuals with whom the patient is closest. Patients included three individuals suffering from neurodegenerative disease (Alzheimer's Disease and Lewy Body Dementia), two of whom exhibited symptoms of CS, and one of whom, D.F., did not exhibit such symptoms. Patients and healthy age-matched controls were administered a series of 2-alternative forced choice (2-AFC) tasks in which they were asked to indicate which of two faces, voices, or names belonged to a famous individual. We found that 2-AFC recognition accuracy for faces and voices was impaired in patients with CS relative to both healthy-age matched controls, and patient DF. However, 2-AFC recognition accuracy for famous names was not impaired in CS patients. Interestingly, patients with CS also tended to be less confident in their recognition judgments and provided fewer accurate semantic facts about each famous individual when presented with that individual's face or voice. The implications from these results are twofold. First, patients with CS exhibit impairments in recognition of faces and voices of famous, non-personally familiar individuals. Second, patients with CS have difficulty accessing person-specific semantic knowledge in response to a perceptual cue (face, voice), but not in response to a lexical cue (name).

1-F-173 Does linear perspective resolve depth ambiguity in biological motion displays?

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Recent studies have successfully used linear perspective to disambiguate otherwise ambiguous

projections of point-light displays. The observation implies that observers are sensitive to linear perspective even though the human body is amorphous, deforms during walking and does not provide obvious cues to linear perspective such as parallel lines, right angles, or texture gradients. However, a perspective camera located half a walker height above ground looks down at the feet and up at the head. We hypothesize that the effect of "perspective" is in fact reflecting a viewing-from-above bias operating on the feet whose motion is much more salient than that of the head. Using a staircase procedure, we measured PSE and slope of the psychometric function relating percentage of perceived facing direction to the amount of perspective (quantified as the visual angle the walker subtends at camera location) at three different vertical camera locations: at the level of the feet, at the level of the head, and half way inbetween. With the camera at the height of the walker's head, visual angle at PSE is 3.8 deg and the slope of the psychometric function is 5.4 %/deg. At half that height PSE and slope are 6.7 deg and 3.2 %/deg, respectively. With the camera at floor level visual angle never converges to a stable value reaching a PSE larger than 45 deg and a slope smaller than 0.6 %/deg at the end of a 80 trial staircase. The results imply that it is not perspective itself, but the projection of the feet seen slightly from above, which disambiguates the facing direction of the walker.

1-F-174 C. elegans response to repeated activation of a polymodal nociceptor requires dopamine and neuropeptide signalling

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The overall objective of this research is to elucidate mechanisms of non-associative learning using C. elegans. We studied the response to repeated activation of the ASH sensory neuron pair, which detect a variety of aversive stimuli, including osmotic pressure, nose touch, and volatile and non-volatile compounds. A strain expressing ChR2 exclusively in ASH allowed for the consistent and discrete delivery of simulated aversive stimuli to worm populations being tracked by real-time computer vision software. In addition to increasing throughput, the optogenetic approach allowed us to prevent sensory adaptation and also specifically activate ASH. Whole-plate blue light illumination elicited backwards crawling (reversal) in 60-70% of the transgenic animals. Reversals persisted with repeated stimulation at a range of ISIs and illumination durations and intensities. Although the probability of a reversal did not decrement, the response latency increased across trials, with greater decrements at shorter ISIs. Repeated stimulation also led to accelerated forward locomotion and a suppression of spontaneous reversals in the periods between stimuli. These behavioural strategies are predicted to facilitate escape from a hazardous area. Mutant analysis of candidate genes identified behavioural phenotypes for dopamine and neuropeptide synthesis mutants. Persistent responding depended on dopamine signalling and increasing response latency required neuropeptide signalling. Current work is aimed at identifying the relevant receptors and their site of action.

1-F-175 Similar maternal behavioral deficit phenotype implicates Luman/CREB3 in the same pathway as Luman-recruitment factor LRF/CREBRF in regulation of the HPA axis in response to stress

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Luman/CREB3 is a transcription factor that is involved in the unfolded protein response (UPR) triggered by stress in the endoplasmic reticulum, while Luman-recruitment factor LRF/CREBRF a binding protein and regulator of Luman. Recently, we have reported a severe maternal behavioral phenotype in the LRF gene knockout null mice accompanied by misregulation of glucocorticoid signaling and prolactin levels. We have proposed that LRF play a key role in the regulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis. Here we report the initial characterization of a Luman gene knockout mouse model, which has severe maternal behavioral deficit in both heterozygous and null

female mice. In an age-matched study, all pups born to null mothers died within 2 days after birth, while 80% pups born to wild type mothers survived till weaning. There was no bias in genotype ratios in pups from heterozygote x heterozygote matings. Histological analysis of inguinal mammary gland showed normal mammary gland development, milk production and ejection in Luman mutant females. A hidden-reward olfactory test found no difference among the three genotypes. Interestingly, the activated form of the Luman protein was detected in most regions of the brain of non-pregnant female mice except the pituitary gland. The auspicious absence of Luman in the pituitary and functional connection of Luman and LRF suggest that both proteins are involved in the same pathway regulating HPA response to stress, which is critical the development of maternal instinct.

1-F-176 Long-range frontal-temporoparietal junction 10-15 Hz coherence predicts attentional control and signifies sensory gating

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Attention allows us to distinguish salient and non-salient events in our environment. The functional role of attention is an efficient gating of sensory inputs that match expected sensory features. Attentional gating is closely associated with the activation of a ventral attention network that entails anteroventral prefrontal cortex (avPFC), anterior cingulate cortex (ACC), and the temporoparietal junction (TPJ). We tested whether the ventral attention network temporally coordinates its activity in relation to the attentional demanding detection of subtle visual events in 5 patients implanted with intracranial electrodes, in one case nearly covering the entire ventral attention network. We found that correct attentional detection of transient sensory events is predicted by the strength of 10-15 Hz phase coherence within a putative network composed by avPFC, dorsal ACC, and ventral TPJ (see fig 1 for a subject with complete coverage). We observed a concomitant beta coherence change of detected vs missed trials (panel A3). Predictive network coherence emerged shortly before event change (time=0 sec) on detected trials and decreased in the missed trials (or vice-versa). These findings directly support attention models that implicate a multi-node ventral attention network that critically gates sensory processing . Our results suggest that this gating is regulated by long/middle range 10-15 Hz phase synchronization of a ventral network and a beta synchronized dorsal frontoparietal network. We speculate that selective coherence may underlie attentional gating of sensory input.

1-F-177 Eye exercises enhance letter recognition and response accuracy in a modified rapid serial visual presentation (RSVP) attention task

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Eye exercises have been prescribed to resolve a multitude of eye-related problems. However, studies on the efficacy of eye exercises are lacking, mainly due to the absence of simple clinical assessment tools. Because of the large overlapping brain networks for attention and eye movements, we used a RSVP task to assess any measurable effects of short-term eye exercises. In the present study, twenty subjects were randomly assigned to control and experimental groups, each of which performed a pre-training RSVP assessment where target letters were rapidly presented. Response time to target letters, accuracy of correctly responding to target letters, and identification of target letters in each of 12 blocks was measured. The experimental group then performed active eye exercises by following a moving target for 18.5 minutes, while the control group performed a task that minimized eye movements for the same length of time. A final post-training RSVP assessment was performed by both groups and response time, accuracy, and letter identification were compared between and within groups both pre- and post-

training. Subjects who performed eye exercises were more accurate in responding to target letters separated by one distractor (ηp^2= 0.020, PBonf=0.050) and were approaching significance when separated by zero target letters (PBonf=0.079), and also in target letter identification (P=0.011) in the post-training RSVP assessment. This suggests that eye exercises are useful in enhancing cognitive performance on tasks related to attention and memory following a brief training period.

1-F-178 Operant intraoral self-administration of high fructose corn syrup in laboratory rats

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The similarities between obesity and drug dependence suggest the hypothesis that "addiction" can develop to food. This hypothesis leads to the prediction that some foods may be "abused" because they are effective in reinforcing behavior leading to their consumption. The current studies in male Sprague-Dawley rats were designed to explore the reinforcing effect of high fructose corn syrup (HFCS); a sweetener associated with overeating and obesity. To this end, a novel method of operant intraoral self-administration (IOSA) was developed. Rats (n=22) received one daily 3-hour IOSA session, whereby responses on a sweetener-paired lever were reinforced by a discrete intraoral infusion of HFCS (25%, 90 µl/inf). Following 3 weeks of IOSA, substitution tests were performed to assess whether operant behavior maintained by HFCS would persist if it was substituted for the non-nutritive sweetener saccharin (0.1% w/v, 90 µl/inf). Using identical procedures, acquisition of IOSA of saccharin was also assessed in a separate group of rats (n=22). It was found that rats acquired and maintained IOSA of HFCS, but not saccharin. In addition, bingeing behavior developed during the initial 90 minutes of access to the solution, but only in rats that self-administered HFCS. A taste reactivity study, and analysis of food intake, suggested that HFCS was self-administered because of its post-ingestional consequences. These data indicate that HFCS has reinforcing properties, and that intraoral self-administration of HFCS can be used to characterize the effects of this sweetener on addictive behaviors.

1-F-179 Roles of procedural variables, housing conditions and stress hormones in place conditioning in rats treated with AM404, an inhibitor of endocannabinoid membrane transport

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Cannabinoid CB1 receptor agonists are self-administered (SA) by and can produce conditioned place preferences (CPP) in animals. The endogenous cannabinoid system and the CB1 receptor in particular have been implicated in reward-related incentive learning, but the role of particular endocannabinoids in reward is less well known. Anandamide (AEA), an endogenous CB1 receptor agonist, is present in reward-related brain areas and is removed from synapses by a membrane transporter (AMT). AM404, an AMT blocker, increases extracellular AEA, supports SA in monkeys and produces CPP in rats under certain conditions. Place conditioning measures drug-reward by repeated pairing of a drug with a context. We hypothesized that Wistar rats conditioned with AM404 would develop CPP to the AM404-paired context. Further, we hypothesized that variability observed at CPP-producing doses may be affected by the injection-conditioning interval, housing conditions or stress hormones. Using an unbiased place conditioning procedure we examined the role of these variables on the outcome of place conditioning with AM404 (0.1-10.0 mg/kg). We found unreliable place conditioning with AM404 (5.0 and 10.0 mg/kg) and no systematic effect of the injection-conditioning interval, housing conditions or stress hormones. Although rats treated with AM404 showed some

evidence of reward-related learning, results were not consistent and procedural variables, housing conditions or inhibition of stress hormone synthesis did not improve the reliability of AM404 reward. (funded by NSERC)

1-F-180 The effect of heroin dependence on the vulnerability to relapse after abstinence

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What is the role of heroin dependence in the vulnerability to relapse after abstinence? The present study explored the effect of heroin dependence on the reinforcing properties of heroin, stress-induced reinstatement and on resumption of heroin self-administration (SA) in non-stressed and stressed rats. Rats SA 0.05 mg/kg/inf heroin on a FR-1 schedule of reinforcement over 10 sessions (3 hrs each). Four hours following the end of each SA session, rats also received 3 injections (SC) of heroin or vehicle. On day 11 of SA, rats self-administered the same heroin dose on a progressive ratio (PR) schedule. After this, they were tested for withdrawal signs precipitated by a low dose of naloxone (0.1 mg/kg, SC). Then, after a 4-day abstinence period, rats received 9 sessions of extinction. The day following extinction, different groups of rats were assigned to four different testing conditions and responding was measured on a PR schedule. Rats were either pretreated with a 0.5 mg/kg IV injection of YOH; or pretreated with 0 or 0.5 mg/kg IV YOH and then allowed to SA 0.05 mg/kg/inf heroin on a PR schedule; or were in a control group. Although, there were group differences in withdrawal, a PR test during dependence did not reveal group differences. Both groups showed reinstatement by YOH, but there were no differences in break point (BP). Similarly, during the test of resumption, there were no group differences in BP and YOH did not alter responding for heroin on a PR test. Relapse was not affected by prior dependence to heroin after a period of abstinence.

1-F-181 Are There Age-Related Changes in Processing of Emotions in Speech?

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Accurate emotion recognition in speech plays a significant role in social interaction. Lexical content and prosody (tone of speech) are chief components of expressing or perceiving emotions in speech. Several studies report an age-related decline in recognizing affective prosody, which cannot be attributed to hearing loss or cognitive decline. Thus, the purpose of this study is to examine age-related changes in processing positive and negative emotions in speech, particularly the role of lexical content and prosody. Twenty-four older adults and twenty-four young adults participated in this study. All participants were native English speakers, reported good health and had good hearing for their age. The stimuli consisted of 50 auditory sentences, where the lexical content and the prosody corresponded to the combination of one of the five emotions: anger, fear, sad, happy and neutral (for instance, angry content in sad prosody). In the end, there were two sentences for each emotion combination. For the experiment, participants were instructed to rate how much they agree the speaker was _(A/F/S/H) on a 6-point Likert scale. The experiment consisted of three tasks: 1) General rating task - to rate the sentence overall 2) Lexical content rating task - to rate only the lexical content 3) Prosody rating task - to rate only the prosody. Preliminary analysis of the prosody task indicates that compared to young adults, older adults have trouble recognizing angry and happy prosody. However, this deficit is more apparent for fear-rating, where they rely greatly on the content.

1-F-182 Symmetrical norepinephrine release during asymmetrical slow-wave sleep in the fur seal

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On land, fur seals predominately display bilaterally synchronized electroencephalogram (EEG) activity during slow-wave sleep (SWS), similar to all terrestrial mammals. In water, however, fur seals exhibit asymmetric SWS (ASWS), resembling the unihemispheric SWS of cetaceans. Previously, we found that cortical acetylcholine (ACh) release is lateralized during ASWS, with greater levels in the hemisphere displaying lower voltage EEG activity, linking ACh release to hemispheric EEG activation. In contrast, cortical serotonin (5-HT) release is not lateralized during ASWS, demonstrating that bilaterally symmetric levels of 5-HT are compatible with interhemispheric EEG asymmetry. The aim of the this study was to measure the release of cortical norepinepherine (NE) across the sleep-wake cycle in the northern fur seal. NE release was measured using in vivo microdialysis in combination with polygraph recordings (EEG, EMG, and EOG). NE levels were determined using high-performance liquid chromatography. Mean cortical NE release was state-dependent. When compared to quiet waking (QW), NE levels were highest during active waking at 146%, decreased during bilateral SWS to 66%, and were minimal during REM sleep at 45%. Cortical NE release was not lateralized during ASWS; NE levels were similar during right and left ASWS at 94% and 95% of QW levels, respectively. Similar to 5-HT, NE release is not lateralized during ASWS, despite the lateralized EEG activation. Our findings indicate distinct roles of ACh, 5-HT, and NE with respect to EEG activation and behavioral arousal.

1-F-183 Influence of Acute Circadian Disruption on the Quantity and Structure of Sleep: A Study with Continuous Local Field Potential Recordings in a Freely Behaving Rat

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Circadian disruption commonly occurs with aging populations and shift work. Acute circadian disruption has been shown to cause a deficit in the retention performance of a rat on the Morris water maze (MWM). There is extensive evidence supporting the theory that sleep plays an important role in memory processing. However, little is known about what aspects of sleep are affected by circadian disruption and how they are related to the behavioural memory retention deficits. As the first step, we investigated whether the quantity and structure of sleep are influenced by a circadian shift. We have continuously recorded local field potentials in hippocampus and prefrontal cortex from freely behaving rats. We have performed offline analysis of the sleep quantity and structure of four animals focusing on 18 days around the shift (split into three epochs; pre-shift, shift and post-shift). We have found that the total quantity of motionless period, slow wave sleep (SWS) and rapid eye movement (REM) sleep was not changed significantly in three out of the four animals (Kruskal-Wallis test and post-hoc multiple comparisons). By contrast, we have found that the distribution of the length of motionless period, SWS and REM events did change across shift and post-shift epochs in three of the four animals (Kolmogorov-Smirnov test). This result suggests that an acute circadian shift influences the structure of sleep rather than the amount of sleep. It also suggests that these changes may be linked to a deficit in a rat's retention performance on the MWM.

1-F-184 Irrelevant stimuli intrude into scalar short-term memory: Experimental and computational approaches

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Previous theoretical treatments of short-term and working memory have proposed the intrusion of irrelevant information into the memory store as a mechanism of interference. Using a vibrotactile delayed match-to-sample memory task, we have demonstrated the encoding of irrelevant stimuli into memory. Additional support for this finding comes from the application of a neurocomputational model of prefrontal cortex to our data.

1-F-185 Measuring memory in Alzheimer's disease in a visual search task

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Alzheimer's disease (AD) affects the hippocampus earlier and more severely than other brain regions, suggesting that tests of hippocampal-dependent memory may track the progress of the disease. The most common test of AD is the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog), which assesses several cognitive functions including memory, as measured by verbal report of word lists. Performance on the memory component of this test may therefore be confounded by language ability. We developed a memory test using visual search that depends on hippocampal function. This modified change detection task requires participants to find changing items ('targets') within flickering images of natural scenes. Remembered targets are found faster than forgotten ones, thus search time is a measure of object-in-scene recall. To determine the utility of this task in measuring memory in Alzheimer's patients, we tested six patients with AD on the ADAS-cog and on the change detection task, across time. Patients were a part of a study involving deep brain stimulation of the fornix. The ADAS-cog scores were correlated with target recall. Whereas the extreme performances matched across tests, the intermediate ADAS-cog scores were associated with a range of performance on the change detection task. These preliminary results suggest that the modified change detection task follows coarse differences in the ADAS-cog measure, and may prove to be more sensitive than intermediate ADAS-cog scores at detecting differences in impairment at early- or intermediate-stage Alzheimer's disease.

1-F-186 Behaviour of larval and adult Drosophila is significantly altered by different commercially available, standard media

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Diet profoundly influences the behaviour of many organisms across phyla. Despite this, many laboratories employ the use of multiple, supplier based food sources for rearing of their animals. We employed several behavioural assays to determine if different food sources alter wild-type Canton S Drosophila melanogaster larval and adult behaviour. We first assessed whether the different food sources altered thermal preference of the third-instar larvae. Using a custom thermal gradient, we determined that larvae reared on Carolina Biological's® formula 4-24 had a significantly lower thermal preference than those larvae reared on Fisher Scientific's® Jazz-mix (16.1+ 4.1 and 18.66 + 4.0, $P<0.05$). Next we determined if these diets altered the motor skills of adults by subjecting them to a geotaxis assay. We observed that a greater percentage of adults reared on formula 4-24 elevated past the halfway point of the vial (4 s after knock-down) than those reared on the Jazz-mix (60.6 + 0.8 and 74.0 + 0.6, $P<0.01$). However, after 55 seconds, the adults performed equally, irrespective of diet. Next we assessed if the diets had any impact on adult learning and memory by employing a modified version of Tully et al., (1985) custom made T-Maze. We observed that adults performed equally well (>80%) on the learning and memory assay when raised on either diet. These results demonstrate that even standard, commercially available diets can profoundly influence the behaviour of wild-type Drosophila. Consequently, these data emphasize the

importance of consistency when rearing laboratory animals.

1-F-187 Phase-amplitude coupling in macaque hippocampus during visual search

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Oscillations in neural populations occur in distinct frequency bands, and these bands may show a higher-order nesting - or cross-frequency coupling - that varies by brain region, cognitive processing, and performance. One well-described example of cross-frequency coupling is the amplitude of gamma oscillations which are modulated by the phase of theta oscillations in the hippocampus of rodents during spatial exploration [1]. Another canonical hippocampal event known as a sharp-wave ripple (SWR) was recently shown to be amplitude-modulated by the phase of oscillations in the high beta/low gamma frequency band, during a similar task in the rodent [2]. If phase-amplitude coupling plays a key role in hippocampal function, it might be evident in other hippocampal-dependent tasks, and independent of species. During a memory-guided search task thought to require hippocampal function [3], we recorded the local field potential (LFP) from the hippocampus of the macaque. During visual search, we observed bouts of theta, and high-frequency oscillations including gamma, high-gamma, and SWRs. We measured theta-gamma phase-amplitude comodulation and observed high-beta/low-gamma phase modulation of the SWR amplitude. Further analysis may reveal the precise temporal coordination of these effects, and whether these phenomena are associated with task performance. [1] Jensen, O. & Colgin, L. L. (2007). Trends Cogn. Sci. 11:267-9. [2] Carr, M. F., Karlsson, M. P. & Frank, L. M. (2012). Neuron 75:700-713. [3] Chau, V.L., Murphy, E.F., Rosenbaum, R.S., Ryan, J.D. & Hoffman, K.L. (2011).

1-F-188 Activation of residual hippocampal tissue in developmental amnesia during remembering and imagining

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The hippocampus plays an integral role in episodic remembering, imagining, and scene construction. There are, however, reports of cases who retain these abilities despite hippocampal damage. Here, we measured activation of residual hippocampal tissue in a developmental amnesic person (H.C.) as she engaged in episodic remembering and imagining of others' experiences. Participants were scanned as they recollected past experiences in response to personal photos ('EM' condition) and imagined others' experiences in response to photos of personally known others ('pToM' condition) and unknown others ('ToM' condition). In a post-scan interview, participants described the events generated in the scanner. Narratives were scored using the Autobiographical Interview procedure. Due to the visually rich photos, internal details were further classified as descriptive (details that describe the visual content of the photo) or elaborative (details that go beyond what is depicted in the photo). Percent signal change was calculated for ROIs of bilateral anterior and posterior portions of the hippocampus. Behaviourally, H.C. was impaired on the elaborative details of EM and pToM events, but not the ToM events. Despite dissociations in behaviour, ROI analyses revealed bilateral anterior and posterior hippocampal activity in all three conditions in H.C. Our results suggest that activation of residual hippocampal tissue does not necessarily reflect intact behaviour. Differences in connectivity between the hippocampus and other brain regions are explored as possible accounts for this discrepancy.

G – Novel Methods and Technology Development

1-G-189 An Electro-Microfluidic Platform for Studying Heavy Metal Toxicity in Nematode Caenorhabditis elegans

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A method to induce and quantify on-demand locomotion in nematode Caenorhabditis elegans through electric fields in a microfluidic environment is here demonstrated in a novel assay for neurobehavioural chemical toxicity. The assay is here employed in a toxicological investigation of environmental pollutants, specifically heavy metals. Worms were grown on plates spiked with AgNO3, CuSO4 or HgCl2 and then scored for locomotory defects with the microfluidic electrotaxis assay. Conventional toxicological endpoints including growth, brood size, lifespan, and fluorescent marker expression were also examined to allow sensitivity comparisons between the different techniques; significantly, our electrotaxis assay displayed sensitivity similar to these others. These results suggest that the microfluidic electrotaxis assay can provide a rapid, sensitive and economical means to detect the neurotoxic effects of heavy metals and other compounds on multicellular eukaryotes.

1-G-190 Extensive Transduction of the Central Nervous System Following A Single Intra-cerebroventricular Injection of Adeno-associated Viral Vectors in Neonatal and Juvenile Mice

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Several neurodevelopmental disorders are potentially treatable via viral vector-mediated gene transfer. Adeno-associated viral (AAV) vectors have been vectors of choice in recent clinical trials in the CNS. Major factors affecting tropism, intensity and cell-type specificity of AAVs include encapsidation of different AAV serotypes, promoter selection, and timing of administration. We evaluated the ability of single-stranded AAV 2/9 vectors to transduce specific cell types in the brain following intra-cerebroventricular injections in mice. AAV2/9 vectors encoding the enhanced green fluorescent protein (GFP) reporter, driven by the cytomegalovirus (CMV) promoter, or the neuron-specific synapsin-1 promoter, were injected bilaterally into the lateral ventricles of mice at postnatal day 5 or 21. GFP immunohistochemistry , 25 days following neonatal and juvenile administration of viral vectors, revealed transduction throughout the entire brain but with different patterns of cell-specific gene expression. Transduction of astrocytes was observed with vectors carrying the CMV promoter at postnatal day 5. In contrast, injection of the same vector on postnatal day 21 resulted in preferential transduction of neurons. Administration of the vector with the synapsin-1 promoter resulted in a widespread neuronal transduction. These results outline efficient methods for gene delivery to the CNS by direct, early postnatal administration of AAVs and highlight the effect of promoter selection and age of administration on the distribution and cell-type specify of AAV transduction in the brain.

1-G-191 Rapid and reversible knockdown of endogenous proteins by peptide-directed lysosomal degradation

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Current approaches to alter levels of endogenous proteins via regulating transcription and/or translation are hindered by many technical difficulties and not clinically feasible. Here we describe a peptide-based method that can rapidly and reversibly knockdown endogenous proteins in intact cells. The peptide consists of the cell membrane penetrating domain, the target protein-binding domain, and the signal that directs the peptide-protein complex into lysosomes for degradation. We demonstrated the versatility and efficacy of the method to selectively knock down α-synuclein or death associated protein kinase 1 (DAPK1) in HEK cells. We then showed that this peptide approach rapidly and reversibly knocked down endogenous DAPK1 in neurons following

excitotoxic/free-radical insults, thereby reducing neuronal damages in primary neuronal cultures. This method may represent a versatile and powerful tool not only for deciphering molecular mechanisms in biomedical research laboratories, but also for developing novel therapeutics for certain pathogenic protein-induced diseases in clinical settings.

1-G-192 Human MiniPromoters for the Brain, Eye, and Spinal Cord; Developed in the Mouse Genome but Delivering the Same Restricted Expression in the AAV Genome

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[1]University of British Columbia, [2]University of Florida, [3]British Columbia Cancer Agency

Small promoters that drive cell-type restricted expression are important for basic research such as delivery of siRNA, and clinical applications such as virus-based gene therapy. Our work is focused on the development of human MiniPromoters (MiniPs) for the brain, eye, and spinal cord. In this study we also tested whether restricted promoters that were developed using single-copy site-specific knock-in to the mouse genome, would exhibit the same expression pattern when used in adeno-associated virus (AAV) MiniPs were designed using computational biology, generated by fusion PCR, cloned to drive EGFP and/or lacZ, and targeted 5´ of Hprt in ESCs from which mice were derived. Expression was analyzed in males at E12.5, and adult brain, spinal cord, and eye. Viral expression of MiniPs was tested in rAAV2 driving hGFP and packaged in AAV2(Quad Y-F). The viruses were injected intravitreally into 4-wk old C57BL/6J mice We have developed 18 novel MiniPs with expression in mouse brain when knocked-in at Hprt. We have further characterized the expression pattern of 15 previously published MiniPs. Altogether, we have identified 8 new MiniPs with expression in the spinal cord, and 17 with eye expression. Three MiniPs with expression in the retinal ganglion-cell layer were tested using rAAV2 and they showed similar restricted expression as observed when knocked-in. We conclude that the computational method of MiniP design, and/or characterization of the promoters using single-copy site-specific integration in the mouse genome, renders them unusually suitable for use in AAV.

1-G-193 CRBMseg: Brain MRI Tissue Segmentation with a Continuous Restricted Boltzmann Machine

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Segmentation of brain magnetic resonance imaging (MRI) volumes into distinct tissue types has several applications, including building population atlases of brain tissue types, guiding surgeons in the operating room, and monitoring anatomical changes in the brain. Existing brain MRI tissue segmentation algorithms such as FAST and SPM5-segment leave room for performance improvements in both processing time and segmentation accuracy; Tsang et al. (2008) tested FAST and SPM5-segment, finding misclassification rates of approximately 10%. We present a novel algorithm for automated brain tissue segmentation on anatomical MRI volumes which employs a continuous restricted Boltzmann machine, called CRBMseg. Trained on a representative data set of 23245 pixels, our algorithm was able to segment brain tissues in a test data set with a misclassification rate of 9% (Figure 1). We present the results of this pilot performance test, and discuss future refinements of the algorithm to incorporate 3D spatial data and integrate it into existing pipelined MRI processing packages.

1-G-194 FlyMAD: A technique for rapid activation of neurons in freely walking flies

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Advanced study of neuronal circuits requires manipulation of neurons in a spatially- and temporally-restricted manner, ideally in a freely behaving animal. Genetic techniques in Drosophila permit a high degree of spatial specificity. Precise temporal resolution requires the control of genetically-encoded tools by external triggers. Optogenetic techniques are difficult to apply in intact flies, due to inadequate transmission of visible light through the Drosophila cuticle. In contrast to visible light, infrared light can penetrate the cuticle, and can be used to activate neurons that have been thermo-sensitized by the expression of TRPA1. Here, we present a technique, called FlyMAD (Fly Mind Altering Device), that allows fast thermo-activation of neurons in flies within a two-dimensional arena. FlyMAD uses a beam of infrared light directed by real-time tracking software to raise the temperature of its target. We demonstrate the efficacy of FlyMAD by activating locomotion neurons that induce the fly to walk backwards.

1-G-195 Time-varying the Onset of TMS Stimulation During Concurrent TMS-fMRI: A method for high temporal resolution explorations of the interactions between brain regions

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Concurrent transcranial magnetic stimulation and fMRI (TMS-fMRI) is a method which allows for a direct examination of the functional connectivity between brain regions. When a TMS pulse is fired, it modulates neural activity at the site of stimulation. This then has task-specific effects on activity in regions interacting with the site of stimulation. We performed a TMS-fMRI study in which we time-varied the onset of TMS pulses with regard to trial onset during a memory encoding task. Eighteen participants were presented with pairs of images, and instructed to memorize the pairs (an associative memory task). The images could either be semantically related or unrelated. Three pulses of TMS (ISI 100ms) were presented to the left dorsolateral prefrontal cortex (L-DLPFC) starting either 200ms, 600ms, or 1000ms into the trial. Time-varying the onset of TMS stimulation for different trials makes it possible to examine which regions are interacting with the stimulated region during discrete time windows. Time and condition (related or unrelated pairs) specific effects were observed in several regions. For example, TMS stimulation during the 200ms condition increased activity in the anterior insula and left supramarginal gyrus for related pairs only, while increased activity for related pairs in the 600ms condition was observed in the caudate nucleus and cerebellum, as well as the posterior regions of the left superior temporal gyrus (a region implicated in semantic processing) This suggests that time-varying TMS-fMRI can be used as a highly temporally specific measure of the interaction between brain regions.

H – History, Teaching, Public Awareness and Social Impacts in Neuroscience

1-H-196 "Are you in pain?" Ethical considerations of first contact with the disorder of consciousness patient

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Recent findings in neuroscience (Cruse et al. 2011, Lancet; Monti et al. 2012, NEJM; Owen et al. 2006, Science) suggest that fMRI is a viable method for detecting awareness in patients thought to be in the vegetative state (VS). This research may open a promising new avenue for developing brian-computer interfaces (Naci et al. 2012, Ann Neurol) that complement the current diagnostic methods for identifying disorders of consciousness (DOC), thereby increasing diagnostic effectiveness in this population. Moreover, this technique may also permit patients, who are behaviorally non-

responsive yet retain preserved cognition, to meaningfully engage in medical decision-making. To date, two reported patients, previously diagnosed as VS, have been able to answer a series of autobiographical binary questions during scanning sessions (Naci et al. in preparation; Fernandez-Espejo et al. in preparation; Monti et al. 2010, NEJM). A natural step forward, therefore, is to integrate these techniques into the standard assessment batteries used by clinicians and medical ethicists One unexplored dimension of this research program is determining what clinical information is immediately relevant to acutely brian-injured patients. If, for example, this technology is used to communicate with DOC patients, what type of questions should initially be asked? We argue that, in principle, clinicians should immediately inquire about the patient's level of physical pain. Doing so satisfies established bioethical norms, and provides clinicians the most relevant information for initial treatment.

1-H-197 Occurrence and profile of injuries among individuals with Alzheimer's disease or dementia in Canada

***Ming-Dong Wang*[1], Catherine Pelletier**[1], **Asako Bienek**[1], **Sulan Dai**[1]
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This study aims to analyse the occurrence and profile of injuries among individuals with Alzheimer's disease or dementia (AD) in Canada. Canadian Community Health Survey-2010 data were used. Respondents aged 35+ were asked if they had AD diagnosed by a health professional and suffered from a serious injury in the last year. SAS EG 5.1 was used for multivariate logistic regression analyses; proportions were weighted to represent the Canadian population. Of the 40,752 respondents (males: 48.5%; 95% CI: 48.2-48.8%; females: 51.5%; 95% CI: 51.2-51.8%), 289 (0.6%; 95% CI: 0.5-0.7%) reported having AD. Of those, 23.8% (95% CI: 14.4-33.3%) reported an injury in the last year, compared to 12.2% (95% CI: 11.6-12.8%) among respondents without AD. Controlling for age, sex, education, marital status, smoking, alcohol use, physical activity, body mass index (BMI), and comorbidity, the odds of injury among respondents with AD were significantly higher than among those without (OR: 4.8; 95% CI: 2.0-11.1). The occurrence of fall-related injuries among respondents with AD was higher compared to those without (20.7%; 95% CI: 11.4-30.1% vs. 4.8%; 95% CI: 4.4-5.1%), and most injuries occurred at home (84.1%; 95% CI: 70.7-98.1% vs. 46.2%; 95% CI: 43.8-48.7%). The odds of injuries increased with comorbid arthritis and asthma, BMI, physical activity, current alcohol use and post-secondary education, and decreased with age, and among female and married respondents. Injuries in respondents with AD were almost 5 times higher compared to those without AD, mostly due to falls, and occurring at home.

IBRO – International Brain Research Organization

1-IBRO-198 Involvement of endothelin ETA and ETB receptors on neuropathic pain following spinal cord injury in rats

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Spinal cord injury (SCI) is a devastating neurologic disorder that compromises major motor, sensory, autonomic functions. Endothelins are a family of peptides that exert their biological effects via distinct receptors, endothelin A (ETAR) and endothelin B (ETBR) that contribute to sensory changes in inflammatory and neuropathic pain. However, their role in nociception following SCI still remains to be elucidated. Adult male Wistar rats had SCI by inflating an embolectomy catheter at T10 level. We evaluated the sensitivity of the animals to mechanical (von Frey monofilaments) and thermal (Hargreaves test) stimulation of the paws on days 2, 7, 14, 21 and 28 after SCI. The frequency of responses to mechanical stimulation of forepaws was unchanged at any time point, but that of hind paws was increased at 14, 21 and 28 days. A significant reduction in withdrawal latency

to heat stimulation of fore paws was detected 7 and 14 days post-SCI and of hind paws at days 14 and 21. The upregulation of ETAR expression in spinal cord was 21 days post injury when compared to sham-operated group, but ETBR expression was not altered. ETAR mRNA level was increased in the spinal cord on days 7, 14, 21 and 28 days and on DRG on the 7th day post-SCI. ETBR mRNA levels were increased in the spinal cord on days 2 and 7 post-surgery but DRG was not altered in the periods analyzed. Our current results suggest that SCI animals develop mechanical and thermal hyperalgesia and ETAR are upregulated after SCI.

1-IBRO-199 MiR-134/LIM Kinase1: how far can this duo modulate neuropathic pain?

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Spinal cord lesions may induce severe neuropathic pain. While more than 8% of the world's population suffers from neuropathic pain, the mechanisms underlying this pain remain unclear. The neuronal actin cytoskeleton is critically involved in morphological plasticity and synaptic reorganization acting as a key player in neuropathic pain mechanisms. LIM Kinase1 (LIMK1) is a protein kinase responsible for actin polymerization by inhibiting Cofilin/ADF activity. LIMK1 expression is controlled by the microRNA, MiR-134 that represses LIMK1-mRNA translation. MiR-134 is considered as a negative regulator of dendritic spine volume and LIMK1 has been reported to promote actin polymerization in dendrites. Moreover, LIMK1/cofilin regulates the insertion and trafficking of the AMPA excitatory glutamate receptors (AMPAR) at the synapse. Therefore, it is likely that miR-134/LIMK1 modulates the transmission of nociceptive information in the spinal dorsal horn. We wanted to investigate the effects of miR-134/LIMK1 on pain sensitization. We investigated miR-134 distribution in the spinal dorsal horn of both sham and neuropathic animals (SNL) at the synaptic level. qRT-PCR analysis showed a decrease of miR-134 expression in neuropathic animals. Intrathecal injection of miR-134 knockdown (miR-134 KD) probes in SNL rats partially alleviates pain. The effect of miR-134 KD transfection on the trafficking of AMPAR was also studied. Taken together, our results suggest that miR-134 down regulation in neuropathic conditions exerts an anti-nociceptive role.

1-IBRO-200 Hiv-Associated Sensory Neuropathy Among A Hospital-Based Cohort In Nigeria: Result Of A Pilot Study

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[1]University of Ilorin

Introduction: Sensory neuropathy is a significant cause of morbidity among patients living with the human immunodeficiency virus (HIV). However, there is a paucity of information on HIV-associated sensory neuropathy in Nigeria in spite of a large disease burden. Objective: The objective of this pilot study was to determine the prevalence of HIV-associated sensory neuropathy among the cohort of patients attending our highly-active antiretroviral therapy (HAART) clinic. Method: Consecutively consenting adults diagnosed with HIV and who were on follow up in our services were recruited. Information was obtained in a standardized manner using an interviewer administered questionnaire. Diagnosis of peripheral neuropathy was done using the well-validated Brief Peripheral Neuropathy Screen which has been used in similar studies. Results: In this pilot study, there were 49 respondents with a mean age of 39.6±10.4 years. Majority of the patients were females (77.6%). Peripheral neuropathy was found in 40.8% of the respondents. There was no significant relationship between presence of peripheral neuropathy and the age, gender, duration of HIV infection and CD4 cell count of the patients. Conclusion: HIV-associated sensory neuropathy is present in a significant number of patients in this hospital-based cohort. However, we were unable to establish a relationship with such variables like age, duration of HIV and CD4 cell count possibly as a result of small sample size.

1-IBRO-201 L-butionine (S,R) sulfoximine effect on oxidative metabolism of substance nigra compacta and striatum and behavior of rats

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Glutathione is the major antioxidant in the living cells. Its deficit has been linked to neurodegenerative disorders like Parkinson´s disease but its role in the etiology of nigral degeneration has been poorly explored. Our aim is to evaluate the effect of nigral L-butionine sulfoximine injection on oxidative metabolism, dopaminergic cells survival and behavior. L-butionine sulfoximine (15 mM) or saline solution was injected into substance nigra. Oxidative metabolism was study 24h and 7days later in substance nigra pars compacta and striatum. Tyrosine hydroxylase inmunohistochemistry was carrying out at 7 days. The animals were evaluated in open field, beam and adhesive removal tests. L-butionine sulfoximine injection cause nigrostriatal glutathione depletion but did not induce change in oxidative metabolism. However a loss in dopaminergic cells was observed. At the same time, animals with glutathione depletion have shown distance traveled diminished in open field and beam traverse tests and poor performance in the adhesive removal test. These results suggest that glutathione depletion may be related to sensorimotor dysfunction.

1-IBRO-202 Effect of trans-caryophyllene on neuropathic pain in an animal model of multiple sclerosis

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Trans-caryophyllene (Tc) is a natural compound present in plants rich in essential oils, such as Cannabis sativa, Cinnamomum spp. and Ocimum gratissimum. These plants have anti-inflammatory and analgesic activities. The aim of the present study was to verify the effect of trans-caryophyllene on neuropathic pain in the experimental autoimmune encephalomyelitis (EAE). Female C57BL/6 mice were immunized subcutaneously with 200 µg of MOG35-55 peptide emulsified in complete Freund's adjuvant. Animals were treated with three doses (3, 10 or 30 mg/kg, p.o) during 26 days. Mechanical hypernociception and the development of the disease were evaluated after EAE induction. In a second moment, other animals received acute oral administration of Tc (10 mg/kg, p.o) on the 6th day after EAE was induced. The action mechanism of Tc was tested using two different drugs 30 minutes before Tc: naloxone (1 mg/kg, i.p) an opioid antagonist, and a cannabinoid antagonist, AM630 (1 mg/kg, i.p) on the 8th day and on the 12th day, respectively. After this period, the animals were observed for clinical signs of EAE. Trans-caryophyllene was able to reduce the hypernociception in this model but did not prevent the development of the disease. Both antagonists were effective in blocking the effect of the treatment with Tc. This compound seems to exert a relevant antihypernociceptive activity by modulating the cannabinoid and opioid systems. In summary, these findings are important because indicate a possible benefic effect of trans-caryophyllene in the treatment of neuropathic pain.

Poster Session 2

A – Development

2-A-1 Role of mTOR pathway in GABAergic maturation in the mouse neocortex

Mayukh Choudhury[1], **Dominique Dufour Bergeron**[1], **Marisol Lavertu-Jolin**[1], **Josianne Nunnes Carrico**[1], **Graziella Di Cristo**[1]
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The mTOR pathway has been implicated in controlling several aspects of neurodevelopment by regulating the rate of protein-synthesis. Mutations in the regulatory components TSc1 and TSc2 of mTOR-Complex1 (mTORC1) cause Tuberous Sclerosis (TSC) in humans. Majority of TSC patients develop neurological problems like seizures, mental retardation and autism. Recent studies investigated the role of mTOR pathway dys-regulation in excitatory cortical cells; however its role in the development of neocortical GABAergic interneurons and the specific contribution of altered GABAergic cells in disease manifestation remain largely unknown. Here, we investigated whether and how Tsc1 knockout perturbs GABAergic circuit development, both in vitro and in vivo. We found that pS6 immunolabeling, a marker of mTORC1 activation, increased specifically in cortical Parvalbumin-positive, Basket GABAergic cells during the peak of their synaptic maturation phase, between the 2nd-4th postnatal week postnatal in vivo. To investigate the role of mTORC1 activation in basket cells, we knocked down TSc1 expression in single basket cells in cortical organotypic cultures prepared from Tsc1-lox mice, by transfecting CRE-GFP during specific phases of postnatal development. Using this strategy, we found that TSc1 knockdown caused a precocious increase in bouton density and terminal branching in mutant cells, which were reversed by Rapamycin treatment. These data suggest that mTOR pathway hyperactivation might affect the timing of basket cell synapse maturation. In vivo studies are currently underway.

2-A-2 Disrupted in Schizophrenia-1 (DISC1) regulates the development of neural connectivity via a novel Dixdc1-actin cytoskeleton pathway

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Schizophrenia is hypothesized to be a neurodevelopmental disorder, arising from abnormalities in neural connectivity. To better understand these disruptions, we are studying one of the best-established schizophrenia risk genes, DISC1. DISC1 plays an important role in regulating connectivity between developing neurons; however, the molecular and cellular mechanisms by which this occurs remain unknown. Using mouse in vitro and in vivo models, we are testing the hypothesis that a novel DISC1-binding partner, DIX domain containing-1 (Dixdc1), is a key regulator of neural connectivity, playing a role in dendrite outgrowth, dendritic spine and synapse formation. Preliminary results demonstrate that decreasing expression of DISC1 or Dixdc1 using shRNA, or inhibiting their interaction reduces dendritic growth, branching, and spine formation. Using a novel technique involving trans-synaptic rabies virus labelling, we have also shown that DISC1-Dixdc1 interactions are required for synapse formation. Furthermore, these studies have been extended to human embryonic stem cells (hESC)-derived neurons to determine whether these results are conserved in a clinically applicable model. Finally, we have preliminary evidence that suggests that DISC1-Dixdc1 may mediate their effects through regulation of the actin cytoskeleton. Together, these experiments suggest DISC1 functions in a Dixdc1-dependent signalling pathway that regulates neural connectivity, revealing a novel signalling pathway that may underlie the disease phenotypes observed in schizophrenia.

2-A-3 Differential mothering produces differences in behaviour and brain gene expression in adult offspring

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Siblings receive differential parental attention in human families and this can affect their development. Differences in maternal care also occur naturally in rat populations, and offspring raised by high vs. low caring dams display differences in their neurological and behavioural phenotypes in adulthood. We studied the effect of differential maternal care received by pups within the same families as well as between different families. We examined anxiety-like behaviours and the response to stress challenge in adult female offspring, as well as the expression of corticosteroid receptor genes (MR, GR), comparing siblings within families and across families. Preliminary results show that rats receiving more maternal care than their siblings, regardless of whether they came from litters reared by high or low caring dams were less anxious and showed increased locomotor activity. They also showed increased mRNA expression of corticosteroid receptor genes (GR and MR) in the hippocampus, an area of the brain associated with stress responsiveness. Ongoing analyses include assessment of both genetic and epigenetic mechanisms among siblings who received differential licking stimulation during early life. This study elucidates the behavioral and neurochemical response to differential maternal care and their relation to one another.

2-A-4 Effects of environmental enrichment on the HPA-axis in a convulsive rat model

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Environmental enrichment (EE) has been associated with decreased vulnerability to neurological and psychological disorders in several species. Following prenatal stress, EE can reduce anxiolytic behavior and restore normal hypothalamus-pituitary-adrenal (HPA)-axis functioning. One approach to restoring this functioning is through the regulation of corticotropin releasing hormone (CRH). CRH has been shown to be a powerful convulsant in animal models and is up regulated following febrile seizures in humans. In this study, we subjected pregnant dams to daily predator exposure stress from gestational day 13-20. Following birth, subsets of these dams and their pups were housed in a larger, 'enriched' environment. On postnatal day 14, rat pups were given an injection of lipopolysaccharide, followed by a subthreshold dose of kainic acid. Behavior recordings of the ensuing seizures allowed us to classify them based on severity (mild, moderate, or severe). Perfusions and blood collections the following day allowed us to observe CRH-immunoreactivity (-ir) in the hypothalamic paraventricular nucleus, as well as measure plasma corticosterone (cort) levels. Overall, EE decreased CRH levels in all pups, independent of seizure status. Post hoc analysis revealed a trend between plasma cort levels and pre- and post-natal conditions in pups experiencing moderate seizure. Correlations among plasma cort levels, CRH-ir, birth weight, and total seizure score for each group suggests differential HPA-axis function dependent on early life exposure. Supported by an NSERC Discovery Grant to TP.

2-A-5 Prostaglandin E2 alters Wnt-regulated cell behaviour in neuroectodermal stem cells

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Prostaglandin E2 (PGE2) is a signaling molecule involved in early brain development and function. Elevated levels of PGE2, due to exposure of exogenous agents during pregnancy, may increase the risk of developing Autism Spectrum Disorders (ASD). We have previously shown that PGE2 and misoprostol, a drug that is a PGE analogue, can alter the behaviour of differentiated neuroblasts by elevating calcium in growth cones and reducing neurite extensions. In this study, we hypothesized that PGE2 elicits functional changes in cell behaviour through the Wnt (Wingless) pathway. Recent studies reveal a cooperative regulation between PGE2 and morphogens such as Wnt in various non-neuronal tissues. We examined the

prospective interaction of these two pathways in mouse neuroectodermal (NE-4C) stem cells. We showed that PGE2 signaling changes Wnt-regulated cell behaviour by increasing cell migration (average speed, path length, and final distance) and modifying cell cycle behaviour (growth rate and split ratio). We also found that PGE2 modulates the expression of specific Wnt-target genes such as beta-catenin and transcription factors Tcf/Lef in a concentration-dependent manner. Furthermore, we determined that PGE2 signaling may interfere with Wnt-induced alterations via the activity of PKA and PI-3K. Overall, our results show that the interaction of PGE2 with Wnt signaling leads to altered behaviour of NE-4C stem cells. These results suggest that abnormal PGE2 signaling may affect early development of the nervous system and potentially contribute to pathology seen in ASD.

2-A-6 Role of mitochondria in GABAergic synapse development

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GABAergic interneurons are a diverse population of neurons that exhibit distinct physiological properties, express diverse neuropeptides and preferentially synapse onto distinct subcellular compartments of their postsynaptic targets. Basket cells are a subtype of GABAergic interneurons that form perisomatic synapses essential for regulating neural networks, and their alterations are linked to various cognitive dysfunctions. Maturation of basket synapses in postnatal cortex is activity dependent, and recent studies have implicated different molecular pathways involved in the process. Here we look at whether mitochondrial dynamics are important for GABAergic perisomatic synapse development. Recent studies have implicated both mitochondrial fission and the calcium dependent transport of mitochondria in excitatory synapse maturation, however, whether these aspects of mitochondrial dynamics are involved in inhibitory synapse development is unknown. Using single cell genetics to perturb different aspects of mitochondrial dynamics such as fission/fusion capabilities, we find that mitochondrial fission may not be important for GABAergic synapse maturation but for its maintenance. Further, deficits in calcium dependent mitochondrial transport in individual basket interneurons, at specific developmental time periods, affect both perisomatic synapse maturation and maintenance. Therefore, our studies so far show that different aspects of mitochondria function are important in distinct stages of GABAergic synapse development.

2-A-7 Role of ENU-3 in neuronal axon guidance in C. elegans

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The ventrally directed migrations of processes from the AVM and PVM touch receptor neurons in the microscopic nematode C. elegans are dependent on attraction towards the UNC-6/Netrin guidance cue expressed in ventral regions of the animal as well as repulsion from the SLT-1/Slit cue expressed in dorsal muscle. In the absence of both cues, the axons fail to migrate ventrally and instead usually go straight towards the head. Interestingly, in the absence of the UNC-6/Netrin receptor, UNC-40/DCC/Frazzled, the defects are less than in the absence of UNC-6, suggesting the existence of a second UNC-6 receptor involved in ventral guidance. We have recently identified a novel putative trans-membrane protein, ENU-3. A strain lacking both functional UNC-40 and ENU-3 had alterations in the guidance of migrations of the AVM and PVM processes towards the ventral side. This finding suggests that ENU-3 may function in an UNC-6 dependent pathway parallel to UNC-40 in controlling migrations towards the ventral regions. UNC-5 is the main UNC-6 receptor involved in guidance of cell and axon migrations towards the dorsal side. enu-3 mutations also enhanced the

motor axon outgrowth defects of a subclass of the DB motor neurons; DB4, DB5 and DB6 in a strain lacking functional UNC-5. We have found that the outgrowth defects of the motor neurons in the absence of either functional UNC-6 or UNC-5 were largely dependent on the presence of the receptor UNC-40/DCC. Strains also lacking functional ENU-3 had additional motor axon outgrowth defects.

2-A-8 Metformin enhances neurogenesis and oligodendrogenesis in the adult brain in a CBP dependent manner

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While endogenous recruitment of adult neural stem cells has been proposed as a therapeutic strategy, clinical approaches for achieving this recruitment are lacking. We previously showed that an atypical PKC (aPKC)-CBP pathway was required to regulate appropriate neural stem cell differentiation in the developing brain (Wang et al., Dev. Cell, 2010). Here, we demonstrate that metformin, a widely-used human drug, promotes neurogenesis and oligodendrogenesis in the adult brain by activating the aPKC-CBP pathway. First, we show that metformin enhances neurogenesis in the forebrain and hippocampus of adult mice, and in so doing, enhances spatial reversal learning in the water maze. This metformin-induced neurogenesis also requires activation of CBP in vivo, as shown using mice haploinsufficient for CBP. On the other hand, the knock-in mice carrying a germline mutation of the CBP aPKC phosphorylation site (S436A) show a significant decrease in the hippocampal neurogenesis. Second, we demonstrate that metformin increases genesis of oligodendrocytes in the corpus callosum and improves morphological structure of corpus callosum after cuprizone-induced demyelination . Thus, metformin, by activating the aPKC-CBP pathway, recruits neural stem cells and enhances neural function, thereby providing a candidate pharmacological approach for brain injury and neurodegenerative disorders.

2-A-9 The Neuroprotective Compound P7C3 Enhances Funtional and Behavioral Recovery Following Neonatal Nerve Injury in a Dose Dependent Manner

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Sciatic nerve injury in neonatal rats results in a significant loss of both motor and sensory neurons. The majority of these neurons die rapidly following nerve injury through a glutamate induced, excitotoxic mechanism. P7C3 has been previously shown to display proneurogenic properties following injury to the CNS, through protecting neurons from apoptosis. However, this agent has not yet been tested in a model of neonatal nerve injury. We sought to assess the possible neuroprotective effects of daily administration of P7C3 for two weeks, and examined regenerative properties following sciatic nerve crush at postnatal day 3. Animals were randomly assigned to one of nine experimental groups. In the first set of experiments, both the spinal cord and DRG cells were characterized following retrograde labeling of the sciatic nerve with FluoroGold (FG) at 1 month following injury. The number of retrogradely labeled motorneurons in vehicle administered controls was reduced to approximately 35%. However, animals directly administered P7C3 followed a dose dependent regenerative response, with an optimal threshold effect occurring at a dose of 20 mg/kg. At this dose, improved regenerative properties were increased to approximately 80%. The second set of experiments analyzed behavioral recovery of locomotion , following P7C3 administration. Endpoint functional analysis consisted of both electrophysiological and myological assessments. Results indicate that animals administered P7C3 displayed significant functional and behavioral recovery as compared to vehicle controls.

2-A-10 Cannabinoid receptor CB2 modulates axon guidance

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Navigation of retinal projections toward their visual targets is regulated by guidance molecules and growth cone transduction mechanisms. Here, we show that cannabinoid receptor 2 (CB2R) is widely expressed throughout the optical pathway during the development of the retinothalamic system. Both the number of filopodia and the surface area of the growth cone (GC) are modulated by CB2R activity in a PKA-dependant manner. Furthermore, Deleted in Colorectal Cancer (DCC), a receptor for the guidance molecule netrin-1, is required for CB2R induced morphological changes of the GC. CB2R agonists induce GC chemorepulsion and conversely, treatment with CB2R inverse agonists increases retinal explant projections length. These effects are specific to CB2R as no change was recorded in transgenic mouse where the gene coding for the CB2R was altered (cnr2-/-). In vivo, a single intraocular injection of CB2R inverse agonist increases retinal projection branch length and induces aberrant projections in some animals. Moreover, in cnr2-/- mice, we report defects in eye-specific segregation of retinal projections in the dorsal lateral geniculate nucleus (dLGN). These findings highlight the modulatory role of endocannabinoids and their CB2R during the formation of the retinothalamic system.

2-A-11 Distinct effects of niche-derived factors on the behavior of adult forebrain neural precursors

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A complex question in the study of adult neurogenesis is how neural precursor cells (NPCs) are regulated by the diversity of molecules present within their niche. The subventricular zone NPC niche contains numerous regulatory molecules, including EGF, FGF, BMP, PDGF, VEGF, SHH and Notch/Delta families; however, because these factors have typically been studied individually, the relative and the combinatorial effects of these factors on NPC behaviors (proliferation, differentiation and survival) remain unclear. Here, our objective was to perform a side-by-side comparison of the above niche-derived extrinsic factors on NPC cultures isolated from the forebrain of adult mice. First, neurosphere cultures were treated and analyzed to assess the effects of these individual factors on NPC proliferation and survival. Second, adherent cultures of dissociated neurospheres were treated with these individual factors and analyzed by Western blotting and immunocytochemistry to measure changes in NPC differentiation. Third, multi-passage experiments were performed to examine long-term effects on NPC expansion and lineage specification. Finally, combinations of factors are currently being tested to determine whether particular factors have additive or dominant effects on NPC behavior. We are currently complementing our in vitro findings using in vivo approaches. These experiments will help reveal which niche-derived factors are the most influential regulators of NPC behavior.

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

2-B-12 Neto2 is a KCC2 Interacting Protein Required for Neuronal Cl- Regulation in Hippocampal Neurons

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KCC2 is a neuron-specific K -Cl- cotransporter that is essential for Cl- homeostasis and fast inhibitory synaptic transmission in the mature CNS. Despite the critical role of KCC2 in neurons, the mechanisms

regulating its function are not understood. Here we show that KCC2 is critically regulated by the single pass transmembrane protein Neuropilin and Tolloid like-2 (Neto2). Neto2 is required to maintain the normal abundance of KCC2 and specifically associates with the active oligomeric form of the transporter. Loss of the Neto2:KCC2 interaction reduced KCC2-mediated Cl--extrusion, resulting in decreased synaptic inhibition in hippocampal neurons.

2-B-13 Widespread expression of the intermediate conductance Ca-activated K channel in central neurons

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Neuronal excitability can be controlled by calcium-dependent activation of small conductance (SK) or big conductance (BK) potassium channels. We recently found that cerebellar Purkinje cells also express intermediate conductance (KCa3.1) potassium channels previously not believed to be expressed in central neurons. Here we examined the expression pattern of KCa3.1 channels across rat and mouse central nuclei. A monoclonal antibody against KCa3.1 generated a single band on Western blots from brain tissue or HEK cells expressing KCa3.1. Immuno-cytochemistry revealed KCa3.1 labeling in the somata of olfactory bulb mitral and granule cells, thalamic relay and inhibitory cells, nRT cells, cortical pyramidal cells in Layers III-V, most cerebellar neurons, and the mes5 nucleus. KCa3.1 immunolabel intensity varied in hippocampus, with strongest to weakest labeling in the order of hilar interneurons, hippocampal interneurons, CA4 > CA3 > CA1 but not CA2 pyramidal cells. Dendritic label was restricted primarily to Purkinje cells, subicular pyramidal cells, and hilar interneurons. Whole-cell patch recordings and single cell RT-PCR confirmed KCa3.1 mRNA in CA1 pyramidal and inhibitory interneurons. These results indicate that KCa3.1 potassium channels are widely expressed in the CNS, with a functional role for most cell types awaiting further investigation.

2-B-14 Deep cerebellar neurons differentially encode inhibitory inputs of Purkinje cells

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The output of the cerebellar cortex is provided by a layer of Purkinje cells that deliver inhibitory projections onto cells in the cerebellar nuclei (CN), which in turn represent the final output of the cerebellum. Under particular circumstances, such as following sudden unexpected peripheral events, part of the CN neurons probably invert the inhibitory input of Purkinje cells to an excitatory output to mediate cerebellar control of fast reflexes. CN neurons have inward currents provided by T-type calcium channels (I(T)) and hyperpolarization-activated HCN channels (I(H)) that allow them to exhibit two different phenotypes of rebound burst discharges (i.e. Transient and Weak rebound burst CN cells). Here, we examine the response of CN cells to physiological patterns of Purkinje cell input obtained during whisker stimulation in vivo using an in vitro slice preparation. Stimulation of Purkinje cell inputs with a 100 sec train of in vivo Purkinje cell firing patterns revealed differential processing in CN Transient vs Weak rebound burst cells. The relation between pre- and postsynaptic firing rates will be assessed to examine the ability for CN cells to use rebound firing responses to encode the firing rate of Purkinje cell inputs. Network simulations comprised of 10 Purkinje cells providing inhibition to a DCN cell model replicated key aspects of the CN cell response, revealing a central role for IT and IH in translating inhibitory input, and the importance of synchrony of Purkinje cell input in determining the final output of CN cells.

2-B-15 Postsynaptic excitability of granule cells is differentially regulated across cerebellar lobules by a Cav3-Kv4 channel complex

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The cerebellum processes input ranging from motor to vestibular signals carried by mossy fibers to granule cells across 10 cerebellar lobules. Motor-related mossy fiber input is conveyed by high frequency bursts and processed in anterior lobules. Vestibular inputs are conveyed as longer spike trains of varying frequencies to posterior lobules. The extent to which afferent input can be differentially processed across lobules is unknown, but a highly uniform trilayer circuit structure implies a role for postsynaptic signal processing. We used in vitro slices of rat cerebellum to test the hypothesis that an interplay between Cav3 T-type calcium and Kv4 A-type potassium currents regulates A-type availability and cell excitability. We find that subunits of the Cav3-Kv4 K complex are differentially expressed in granule cells across cerebellar lobules. A-type current is widely expressed but T-type current is expressed a higher levels and with an inactivation voltage (Vh) left shifted by 15 mV in posterior cells. A-type current availability is thus increased in posterior cells, reducing the gain of firing. The effects of a Cav3-Kv4 interaction are thus consistent with encoding a wide frequency range in posterior cells and burst input in anterior cells, revealing differential signal processing across cerebellar lobules.

2-B-16 Low voltage activation of BK calcium-activated potassium channels by a novel complex with T-type calcium channels

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Calcium-activated BK potassium channels regulate action potential repolarization through a molecular association with high voltage-activated calcium channels. We examined the potential for low voltage-activated Cav3 T-type calcium channels to interact with BK channels when expressed in tsA-201 cells and in rat medial vestibular neurons (MVN) in vitro. Expression of the channel α-subunits alone in tsA-201 cells was sufficient to enable Cav3 activation of BK current. Cav3 calcium influx induced a 50 mV negative shift in BK activation voltage, an interaction that was blocked by Cav3 or BK channel blockers or high internal EGTA. Cav3 and BK channels coimmunoprecipitated from lysates of tsA-201 cells or rat brain, with Cav3 channels associating with the transmembrane S0 segment of the BK N-terminus. BK channel activation was closely aligned with Cav3 conductance in that BK current shared the same low voltage dependence of Cav3 activation, and was blocked by voltage-dependent inactivation of Cav3 channels. The Cav3- BK interaction was found in a subset of MVN neurons by activating near -50 mV to contribute to spike repolarization and gain of firing. Together the results identify a novel Cav3- BK signaling complex that enables BK activation over a wide range of membrane potentials according to the unique voltage profile of Cav3 calcium channels.

2-B-17 Dynamic wiring of synapses in a memory trace: Activity-driven expression of a synaptogenic protein in a novel mouse model enhances memory

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Synaptic plasticity, the capacity of neurons to change the strength of their connections with experience, provides a cellular mechanism for learning and memory. In order to perform complex behaviors, specific wiring changes must occur at the structural and biochemical level. One class of synapse-organizing molecules, SynCAMs (Synaptic Cell Adhesion Molecules), not only direct the formation of synapses, but influence synaptic ultrastructure, plasticity, and memory formation. Studies examining the dynamic nature of synapse-

organizing proteins in vitro and in vivo activity allow us a better understanding of experience-dependent wiring of neuronal networks. In primary neuronal culture, SynCAM1 undergoes dynamic changes in surface expression during activity-dependent plasticity paradigms. This provides a mechanism for our studies in slice electrophysiology in animals with SynCAM genetically manipulated showing alterations of LTD. New focus on transgenic mouse models permitting control over SynCAM expression allow us to study the link between synaptic and behavioral changes. While constitutive overexpression of SynCAM 1 decreases spatial memory performance, we have preliminary data showing that select manipulation of SynCAM 1 levels in neurons active during memory formation yields memory enhancements. This work represents not only the impact of the role of cell adhesion molecules in synaptic plasticity, but also prepares for testing the wiring of circuits engaged during memory formation, leading to changes on a systems level.

2-B-18 N-acetyl-aspartyl-glutamate (NAAG) is a subunit selective antagonist at NMDA receptors and is modulated by protons

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N-acetyl-aspartyl-glutamate (NAAG) is one of the most abundant peptides in the central nervous system and substantial data support the idea that it modulates glutamatergic neurotransmission. However, the mechanism of action of NAAG on N-methyl-D-aspartate receptors (NMDARs) is not fully understood. Therefore, it is crucial to further investigate the physiological role of NAAG, particularly at NMDARs. It is speculated that the function of NAAG depends on NMDAR subunit composition and is a selective antagonist at extra-synaptic GluN2B-containing NMDARs. There is also some evidence that the affinity of NAAG for NMDARs increases as the pH is lowered. To determine NAAGs specific site of action a pharmacological paradigm was designed to discriminate between intra-vis-à-vis extra-synaptic NMDARs. NAAG significantly reduced the amplitude of isolated extra-synaptic NMDAR whole-cell currents, suggesting that NAAG antagonizes GluN2B NMDARs. To further confirm whether NAAG exhibits subunit specificity, HEK-293 cells will be transfected with recombinant GluN1 in combination with GluN2A or GluN2B subunits. To determine whether the potency of NAAG is pH dependent the behaviour of NAAG dose-inhibition curves on NMDARs at various pH values were characterized on both acute brain slices and HEK-293 cells. It was observed that the potency of NAAG on NMDARs increases with lower pH. Determining the subunit selectivity of NAAG is beneficial in both minimizing the side effects of full NMDAR inhibition and in the development of novel therapeutics and prevention of cell death during ischemic stroke.

2-B-19 A novel complex between T-type calcium channels and calmodulin

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T-type calcium channels provide an important contribution to the pattern of spike output. Responding appropriately to the entry of calcium ions into a cell often involves a host of calcium-dependent second messenger systems. A primary receptor for intracellular calcium is Calmodulin (CaM), a molecule that binds calcium and then acts as a second messenger or even as a feedback device to further modify the nature of calcium entry by a stimulus. CaM has been shown to link directly to each of 4 different high voltage-activated calcium channels (N-, L-, P/Q- and R-type) to respond to calcium influx directly at its source. But these interactions could not account for how neurons respond to stimuli in the voltage range subthreshold to spike dischsarge. Through bioinformatics, biochemical in vitro binding assays, and FRET spectral microscopy, we show that CaM also forms a molecular association with low voltage-activated calcium channels of the Cav3 T-type family. This is important in identifying a means

by which second messenger systems that respond to CaM can be activated in the subthreshold range to control signal processing, nuclear transcription, and spike output in neurons.

2-B-20 Altered neuron-glia interactions at neuromuscular junctions of beta2-laminin deficient mice

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Synaptic laminins are important for the formation and organization of the neuromuscular junction (NMJ). In â2-laminin deficient mice (â2-/-), NMJs have fewer active zones, dispersed synaptic vesicles and defective synaptic transmission. Intriguingly, these mice also exhibit aberrant glial organisation where perisynaptic Schwann cells processes (PSCs), glial cells at the NMJ, invade the synaptic cleft. This glial disorganization may contribute to the synaptic defects since PSCs are known to regulate NMJ stability, synaptic activity and plasticity. The aim of this work was to characterize PSCs activity following â2-laminin ablation. Intracellular recordings of endplate potentials on P14-16 mice Soleus NMJs showed that â2-/- NMJs release less neurotransmitter than wild-type (WT). The ability of PSCs to detect synaptic transmission was also reduced in â2-/- NMJs as revealed by smaller Ca2 responses evoked by high frequency motor nerve stimulation (HFS) and by fewer responding cells. This reduced PSCs excitability could be due to an altered glial muscarinic receptor activation as revealed by smaller Ca2 responses and fewer responding cells to local application of muscarine while ATP-induced responses were similar to WT. Consistent with the Ca2 -dependent regulation of synaptic plasticity by PSCs, we observed that HFS induced larger long term potentiation of transmitter release at WT NMJs than in â2-/-mice. Altogether, these results suggest that neuron-glia interactions are altered in â2-laminin deficient mice, with characteristics often observed at denervated NMJs or in aging.

2-B-21 The amyloid precursor protein intracellular domain regulates synaptic transmission and plasticity

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The processing of amyloid precursor protein (APP), which plays a key role in the development of Alzheimer disease, produces three different products: the APP extracellular domain, the amyloid-beta peptide and the amyloid precursor protein intracellular domain (AICD). After cleavage, the AICD is released into the cytoplasm of neurons, where it is believed to modulate the intracellular calcium concentration. Since deficits in synaptic transmission could be caused by deregulated calcium concentrations, we investigated whether AICD can affect synaptic transmission and plasticity in hippocampal neurons. We found that overexpression of AICD in CA1 neurons leads to a decrease in evoked AMPA-receptor and NMDA-receptor dependent synaptic transmission. Interestingly, AICD expressing neurons fail to induce long-term potentiation (LTP) after applying a LTP pairing protocol, but instead induce long-term depression. The AICD contains a caspase cleavage site and mutating this cleavage site is sufficient to prevent the effect of AICD on synaptic transmission. Our results indicate that AICD induces deficits in synaptic transmission and plasticity.Finding the cellular and molecular mechanisms underlying these effects might help understanding early impairments in neural function in Alzheimer disease.

2-B-22 Accelerated maturation of an auditory synapse in LIMK1 knockout mice

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Auditory brainstem neurons underlying sound localization undergo significant remodeling during development. The calyx of Held, which originates from cells of the ventral cochlear nucleus, is a large

glutamatergic nerve terminal that innervates a single principal cell of the medial nucleus of the trapezoid body (MNTB). Before hearing onset (~P12), the calyx is spoon-shaped but by P16, the morphology has transformed into a digitated finger-like claw structure. In parallel, the calyx of Held-MNTB synapse transforms functionally into a more rapid and reliable synapse due to pre- and postsynaptic changes associated with neurotransmitter release. The precise mechanisms underlying the morphological maturation remain unknown. As a first step to unravel this process, we combined anterograde tracing and confocal imaging in brainstem slices taken from young and mature wild-type and LIM kinase 1 (LIMK1) knockout (KO) mice. LIMK1 regulates actin cytoskeletal dynamics by phosphorylating and consequently deactivating cofilin; a known depolymerizer of F-actin. Our findings show at mature ages (P17/18), calyx morphology is similar between in wild-type and LIMK1 KO mice based on gross morphology, surface area and volume. Remarkably however at young ages (P9/10), calyces from LIMK1 KO mice were highly digitated similar to mature calyces. Electrophysiology to examine functional maturation in LIMK1 KO mice is currently being performed, but these preliminary findings are the first to implicate LIMK1 as a major player in regulating the morphological development of the calyx of Held.

2-B-23 Regulation of metabotropic glutamate receptor functioning in Huntington's Disease

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Group I metabotropic glutamate receptors (mGluRs) play an important role in the pathophysiology of Huntington's Disease (HD), a devastating neurodegenerative disorder caused by a polyglutamine expansion in the huntingtin (Htt) protein. Our lab has shown that Group I mGluRs interact with mutant Htt and cause selective uncoupling of mGluR5 signalling. The Htt interacting protein optineurin (OPTN) causes inhibition of mGluR1 signaling and increases interaction between Htt and mGluR1. Moreover, mutant Htt enhances OPTN-mediated inhibition of mGluR1 signaling. OPTN also binds to the small GTPase Rab8, functioning to enhance Htt recruitment to Rab8 positive vesicles. Rab8 interacts with the C-terminal tail of mGluR1a in an agonist dependent manner, a complex which is regulated by OPTN. Rab8 also interacts with Htt, and Htt is present on Rab8 positive membrane vesicles that may regulate receptor trafficking. Therefore, the current studies tested the hypothesis that Htt/OPTN/Rab8 interactions play a critical role in regulating Group I mGluR function and signaling in HD. We confirmed that mGluR1 interacts with Htt and demonstrated that mGluR5 interacts with Htt by co-immunoprecipitation from cortical, hippocampal and striatal lysates derived from wild-type C57 mice. We also confirmed interaction of mGluR1 with Rab8 and demonstrated interaction of mGluR5 with Rab8. Furthermore, overexpression of the E50K OPTN mutant altered mGluR1 ERK signalling. Results of these studies will help further understanding of Group I mGluR signalling and mGluR interacting proteins in HD.

2-B-24 Cav3 T-type calcium channels become sodium-permeable using an alternate extracellular turret outside the selectivity filter

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T-type (Cav3) channels are categorized as voltage-gated calcium channels but uniquely have a lower voltage range for activity and bear faster kinetics that is more akin to sodium channels.We illustrate that invertebrate Cav3 T-Type channel can be sodium channels, becoming permeant to monovalent ions through exon splicing of extracellular "turret" (S5-P) residues in Domain II of the four domain channel. The sodium permeant T-Type channel is the only splice isoform expressed in the snail heart and contributes to half of the expressed T-type channels in the snail brain. Unique splicing of turret residues in Domain II is conserved

amongst invertebrate T-type channels and likely was the ancestral state, providing T-type channels a capacity to serve as the pacemaking sodium current in the primitive heart and brain in lieu of sodium channels, and could likely substitute for voltage-gated sodium channels lacking in many invertebrates. Invertebrates generate sodium permeable Cav3 T-type channels without altering the invariant ring of charged residues in the selectivity filter that governs calcium selectivity, which are always EEEE in Cav1 and Cav2 channels and EEDD in Cav3 channels. Altered arrangements of residues in T-Type channels provide a capacity for permeation of sodium and potassium ions with cassette replacement of one of four extracellular turret regions. T-Type channels, a primary pacemaker for the brain and heart, are sodium channels veiled with extracellular turret residues enabling them to masquerade as calcium channels.

2-B-25 The role of PAK signalling in synaptic transmission and plasticity using a tetracycline system in mice

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Neurodevelopmental disorders including autism, Alzheimer's disease and intellectual disability are among the most devastating deficits of mental and neurological diseases. These brain diseases are associated with a diversity of potential causes, including single gene mutations. PAKs (p21-activated kinases) 1-3 are a family of serine/ threonine protein kinases that are target enzymes of Rho small family GTPases and central regulators of actin cytoskeleton and neuronal morphology. In vivo studies reveal that PAKs are involved in synaptic and behavioural plasticity. Mutations in the PAK gene are implicated in various brain diseases however we do not understand how these mutations cause synaptic and behavioural deficit. We employ a tetracycline inducible system where the dominant negative PAK3 mutation can be spatiotemporally modulated. We found that mutant PAK3 mice had profound impairments in spatial and associative memory. Furthermore, the learning deficit in the mutant mice can be rescued with a tetracycline analog that blocks the expression of the mutant PAK3 transgene, which suggests that the memory impairments are not perturbed at development and are caused by deficits in mature synapses. We showed that mutant mice had reduced basal synaptic strength and plasticity that were not due to alterations in presynaptic function. Our data indicate that the molecular pathways through which PAK3 may mediate the Rho signalling process through cofilin dependent actin regulation in the cortex and hippocampus has a central role in the regulation of cognitive and synaptic function.

2-B-26 Mechanisms of septin 5-mediated inhibition of neurotransmitter release

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Neurons communicate at chemical synapses via exocytosis of synaptic vesicles containing neurotransmitter. Exocytosis occurs when vesicle and plasma membranes fuse, a process mediated by the interaction of SNARE proteins. Protein interactions with SNARE proteins can therefore influence exocytosis. Septin 5, a filamentous cytoskeletal protein, binds the SNARE protein syntaxin 1A. Septin 5 is expressed predominantly in the brain where it associates with synaptic vesicles, prevents close docking of synaptic vesicles at the plasma membrane, and inhibits exocytosis. However, the specific mechanism underlying the inhibition of exocytosis by septin 5 is unknown. The current study aims to map the region(s) of septin 5 responsible for binding to syntaxin 1A. Intriguingly, two sequences found within septin 5 resemble sequences found in the SNARE-binding protein complexin. Once the binding regions have been characterized, mutant septin 5 lacking the binding region will be expressed in septin 5 -/- neurons to examine the role of this interaction in the regulation of SNARE mediated neurotransmission. This study will provide important advances in our

understanding of the mechanisms regulating exocytosis and neurotransmitter release.

2-B-27 Protein kinase C enhances peptide secretion by regulating voltage-gated Ca2+ channels and vesicle priming in neuroendocrine cells

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A transition from quiescence to periods of increased excitability and secretion is typical of neuroendocrine cells, and is often conferred by protein kinase-dependent phosphorylation. A well-examined system for studying these processes is the bag cell neurons of the marine mollusc, Aplysia. Upon stimulation, these neuroendocrine cells undergo an afterdischarge resulting in hormone secretion to initiate reproduction. During the afterdischarge, protein kinase C (PKC) evokes the membrane insertion of a separate voltage-gated Ca2 channel class. To examine the contribution of these channels to peptide secretion, whole-cell recordings of fura-loaded cultured bag cell were taken, allowing for measurement of secretion, with capacitance tracking under voltage-clamp and intracellular Ca2 with fluorescence microscopy. Pretreatment with 100 nM of PMA, a PKC activator, resulted in a two-fold increase in membrane capacitance to a 1-min train stimulus. Disruption of the actin cytoskeleton with 10 µM latrunculin, to prevent channel insertion, attenuated this effect. To test if PKC influences the priming/trafficking of secretory vesicles, PMA was applied after whole-cell breakthrough, which disrupts Ca2 channel insertion. When added online, PMA significantly increased the train-induced capacitance change and prevented secretion rundown to repeated trains. Thus, PKC prepares neurons for prolonged secretion by enhancing Ca2 channel function and vesicle priming. Consequently, PKC serves as a fundamental regulator of neuronal function to control reproduction and ensure species propagation.

2-B-28 Novel synapses in the adult CNS: Synaptic NMDAR currents in mature spinal lamina I neurons are predominantly mediated by the GluN2B and GluN2C/D NMDAR subtypes

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Activation of NMDA receptors (NMDARs) is critical for both physiological mechanisms of synaptic plasticity and pathophysiological mechanisms of hyperexcitability in the brain and spinal cord. There are four genetically-encoded GluN2 (A - D) NMDAR subtypes that generate heterogeneity in NMDAR function and modulation. Here, we made whole-cell voltage-clamp recordings from lamina I neurons in acute spinal cord slices of adult (350 - 450 g) Sprague Dawley rats. Our recordings of synaptic glutamatergic currents as miniature excitatory postsynaptic currents (mEPSCs) revealed a rapid mEPSC component mediated by AMPA receptors (blocked by CNQX) and a slow mEPSC component mediated by NMDARs (blocked by D-APV). We characterized the NMDAR mEPSC component in lamina I neurons held at +60 mV and found that treatment with 1 uM Ro25-6981 (GluN2B antagonist, n=12), 10 uM DQP-1105 (GluN2C/D antagonist, n=8), or 3 uM TCN-201 (GluN2A antagonist, n = 5) reduced NMDAR mEPSCs by 65%, 25% and 12%, respectively. From these findings, we conclude that the majority of synaptic NMDAR currents in lamina I neurons are mediated by GluN2B rather than GluN2A, in contrast to the brain, where functional NMDARs are predominantly mediated by GluN2A in adult synapses. Furthermore, our results provide the first evidence for slow-decaying GluN2C/D-mediated synaptic NMDAR currents in the adult nervous system. As lamina I projection neurons output directly to brain pain networks, both synaptic GluN2B and GluN2C/D NMDARs are potentially novel molecular therapeutic targets for treating pain.

2-B-29 The role of ROS signalling in AMPA and NMDA receptor down regulation within anoxic turtle brain

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The western painted turtle (Chrysemys picta bellii) overwinters without oxygen for months, making it the most anoxia-tolerant terrestrial vertebrate. Unlike mammals, turtle neurons are able to avoid lethal anoxia mediated increases in intracellular calcium through down regulation of N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (NMDAR and AMPAR) whole-cell currents. A possible biological signal to bring about these rapid changes is a decrease in reactive oxidative species (ROS) that occurs during anoxia. To determine the role of ROS signalling in receptor regulation NMDAR and AMPAR evoked whole cell current amplitudes were observed under varying conditions of oxygen and ROS manipulation. NMDA and AMPA receptor current amplitudes remained unchanged over the course of 90 minutes of normoxia but were decreased during anoxia by 40% and 59%, respectively. Pharmacological reduction of ROS levels under conditions of normoxia using the scavengers N-2-mercaptopropionylglycine (MPG) and n-acetylcysteine (NAC) did not bring about a decrease in NMDA receptor currents similar to anoxia, it increased current amplitudes by 101% and 77%, respectively. Under normoxic conditions H2O2 application mildly decreased NMDAR currents by 19%. ROS manipulation under normoxic conditions had no effect on AMPAR currents. Decreases in both receptor currents brought on by anoxia were not reversed by H2O2 addition. We conclude that the down regulation of NMDAR and AMPAR currents during anoxia is not directly mediated by decreases in ROS levels.

2-B-30 The absence of p75 neurotrophin receptor alters the population of Iba1-immunopositive macrophages in the injured dorsal root ganglia of adult mice

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The aim of this study was to determine the effects of glial and monocytic cell activation in the injured dorsal root ganglia (DRG) of adult mice lacking a functional p75NTR (p75-/-), compared to age-matched wild type mice (i.e., C57Bl/6N and p75 /). We tested two different injury models (i.e., partial sciatic nerve ligation and mono-iodoacetate (MIA) injection into hind footpad) with 1 and 2 week recovery periods in 2-3 month old p75-/- and wild type mice. Similar to previous reports, our results show a significant difference in the populations of Iba1-immunopositive macrophages between ipsilateral and contralateral (and uninjured) DRG of adult wild type mice following a partial sciatic nerve ligation. In contrast, compared to wild type mice, preliminary results revealed a significant increase in the percentage of area occupied by Iba1-immunopositive cells in the contralateral DRG of adult mice lacking functional p75NTR at 1 week post-nerve ligation. There were no significant differences between ipsilateral, contralateral p75-/-, and wild type mice at 2 weeks post-nerve ligation or at 1 week post-MIA injection. At 2 weeks post-MIA injection, there was a significant increase in the percentage area occupied by Iba1-immunopositive cells in the ipsilateral DRG of p75-/- mice compared to ipsilateral DRG of wild type mice. These data suggest that p75NTR plays an important role in maintaining the appropriate immune response following injury to the peripheral nervous system.

2-B-31 Shaping the behaviour of heteromeric kainate receptors

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Kainate receptors (KARs) are thought to assemble primarily as heteromeric complexes at glutamatergic synapses. Interestingly, most KAR-mediated synaptic currents exhibit slow and variable deactivation kinetics, in contrast with the fast gating properties observed with recombinant KARs. To date, emerging evidence suggests that heteromerization of different subunits, as well as

their association with auxiliary proteins, underlie some of these differences. Despite this, it remains to be understood how the neurotransmitter, L-glutamate, triggers prolonged KAR activations. Here, we investigated the functional and stoichiometric properties of recombinant heteromeric KARs assembled from the two most widely expressed subunits, GluK2 and GluK5. To do this, we used a combination of outside-out patch electrophysiology and a fluorescent subunit counting technique to examine their functionality and assess their stoichiometry. As expected, higher degrees of heteromerization were correlated with slow deactivation kinetics and higher responsiveness to the agonist, AMPA. Subunit counting experiments revealed that the stoichiometry of GluK2/GluK5 heteromers is constrained. Consequently, these receptors display functional properties that are distinct from their homomeric GluK2 counterparts, namely their ion-independent gating, which is consistent with a heterodimeric assembly of the subunits at the level of the ligand-binding domain. Here, we investigate how the apparent agonist and ion concentrations explain the behaviour of native heteromeric KARs

2-B-32 Crosslinking the kainate receptor ligand-binding domain dimer interface prevents access to the main open state

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Ligand-gated ion channels exhibit electrophysiological responses with an initial peak that decays to equilibrium in the continued presence of agonist. The decay process is dependent on receptor desensitization leading to the common assumption that prevention of response decay is achieved by blocking desensitization. At the single-channel level desensitization is defined as a "long-lived, agonist bound shut state". Therefore, it is theoretically possible to have a receptor that desensitizes and still produces non-decaying currents. The ligand-binding domain dimer interface of kainate-type glutamate receptors (KARs) is thought to regulate receptor desensitization. By crosslinking the dimer interface we investigated its role in KAR desensitization. Although this mutation produced currents in outside-out patches that were non-decaying they were also 10X smaller than wild-type. Three separate analyses of single-channel conductance revealed that this was due to the inability of the mutant KAR to access the wild-type main open state (30 pS). This is in stark contrast to mutations and treatments of glutamate receptors that block desensitization and trap receptors in the main open state for the entirety of agonist application. Single-channel analysis showed that cross-linked KARs have similar shut states as wild-type demonstrating that the mutant receptor undergoes desensitization. This study identifies a novel role for the dimer interface in controlling KAR subconductance levels and reaffirms that changes in macroscopic decay do not imply changes in receptor desensitization.

2-B-33 Anoxia-mediated activation of protein kinase C reduces Ca2+-activated K+ channel open probability in turtle cerebrocortex

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In mammalian brain, anoxia induces hyper-excitability and cell death; however, the western painted turtle Chrysemys picta bellii is anoxia tolerant and in response to low oxygen stress undergoes large-scale metabolic depression. In cortical pyramidal neurons this involves an arrest of N-methyl-D-aspartate receptor (NMDAR) and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor (AMPAR) currents and an increase in γ-aminobutyric acid receptor (GABAR) currents. In a search for other oxygen-sensitive channels we discovered a Ca2 -activated K channel (KCa) that exhibited a decrease in open probability (Popen) in response to anoxia. Anoxic decreases in KCa channel Popen ceased upon patch excision indicating regulation by cytosolic factors. The inclusion of the potent PKC inhibitor chelerythrine

prevented the anoxia-mediated decrease in Popen (anoxic 0.08 ± 0.02 to anoxic plus chelerythrine 0.45 ± 0.08) while drip application of phorbol 12-myristate 13-acetate (PMA) a PKC activator decreased Popen during normoxia (from normoxic 0.4 ± 0.05 to PMA 0.1 ± 0.02). Anoxia results in a depolarization of turtle pyramidal neurons (~8 mV) and an increase in cytosolic [Ca2]; therefore, KCa arrest is likely important to prevent Ca2 activation during anoxia and to reduce the energetic cost of maintaining ion gradients. We conclude that turtle pyramidal cell KCa channels are oxygen sensitive channels regulated by PKC and are likely the reptilian analog of the mammalian large conductance Ca2 -activated K channels (BK channels).

2-B-34 Failure of Chronic Fluoxetine Treatment to Enhance Plasticity in the Auditory Cortex (A1) of Mature Rats

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Recent reports have suggested that chronic treatment with the selective serotonin re-uptake inhibitor (SSRI) fluoxetine can restore juvenile-like synaptic plasticity in the cortex of mature rodents. We examined this question by assessing long-term potentiation (LTP) in the thalamocortical auditory system of adult rats; levels of LTP in this system show a characteristic decline during early postnatal life. Adult rats were chronically treated with fluoxetine (administered in the drinking water, 0.2 mg/ml, four weeks of treatment). Electrophysiological assessments were conducted using an anesthetized (urethane) in vivo preparation, with LTP of field potentials in A1 induced by theta-burst stimulation of the medial geniculate nucleus. We find that, compared to water-treated control animals, fluoxetine-treated rats fail to express higher levels of LTP and, in fact, show a trend toward reduced levels of potentiation of both thalamocortical and intracortical synapses in A1. Bioactivity of fluoxetine was confirmed by a reduction of weight gain during the four-week treatment period. We conclude that chronic fluoxetine treatment fails to enhance LTP in the rat thalamocortical auditory system. Further, these results bring into question the general effectiveness of SSRIs to enhance plasticity of forebrain synapses.

2-B-35 Glial cell excitability and interactions with synapses are altered during aging

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Synaptic communication in the nervous system is altered in aging. In adults, synaptic communication is a process known to be regulated and modulated by glial cells. However, very little is known regarding changes that take place in the glial regulation of synaptic transmission and plasticity during aging. The goal was to study changes in neuron-glia interactions during aging. We used the mouse neuromuscular junctions (NMJs) of the levator auris longus (LAL) muscle of old (620 days) and adult NMJs (90 days). Using immunohistochemistry labeling of pre-, postsynaptic and glia, we observed typical changes occurring during synapse weakening. Electrophysiological recordings of synaptic transmission revealed a lack in aged NMJs of short- and long-term potentiation induced by trains of nerve stimulation at 100Hz, while synaptic depression remained unchanged. We used Ca2 imaging to monitor perisynaptic Schwann cells (PSCs) activity at the NMJ, glial cells at this synapse. We found that the amplitude of PSC Ca2 responses at old mice NMJs induced by motor nerve stimulation were smaller than in adults. This weakened glial excitability may be due to a reduced muscarinic activation as revealed by smaller muscarine-induced Ca2 responses and reduced effect of muscarinic receptor antagonists at aged NMJs compared to adult ones. As a whole, given the importance of glial calcium activity for proper information processing in adult brain, our work suggests that perturbed neuron-glia interactions during aging could contribute to the alteration of synaptic function during aging.

2-B-36 Tranexamic acid inhibits N-methyl-D-aspartate receptors

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Background: Tranexamic acid (TXA) is an antifibrinolytic drug widely used to prevent excessive blood loss during surgery. We have previously shown that TXA is a competitive antagonist of glycine receptors. Glycine is a co-agonist of N-methyl-D-aspartate receptors (NMDARs). Therefore, we hypothesized that TXA can inhibit NMDARs by interacting with the glycine binding site. Methods: Primary cultures of hippocampal neurons were prepared from embryonic mice. Whole-cell voltage clamp techniques were used to record NMDA-evoked currents in the absence and presence of TXA. All data are expressed as mean ± SEM. Results: TXA inhibited NMDA-evoked currents (1 - 1000 mM) in a concentration-dependent manner (IC50 = 35.5 ± 4.1 mM). Increasing the extracellular glycine concentrations enhanced the percentage block of NMDARs by TXA (Glycine 0.3 µM: 21.4 ± 4.9 %, Glycine 3 µM: 38.8 ± 5.7 %). Conclusion: This is the first evidence showing that TXA inhibits NMDARs potentially via an interaction with the glycine binding site.

2-B-37 Evidence of microglial activation in anterior cingulate cortical white matter of depressed suicides

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Previous work conducted by our group showed that white matter astrocytes in the anterior cingulate cortex (BA24) were hypertrophic in depressed suicides compared to matched non-psychiatric controls. This phenotype may reflect astrocytic reactivity to local inflammation. Given that this phenomenon is likely to be mediated by upstream microglial signalling, the major objectives of the present study were to measure the expression of microglial marker IBA1, and to morphologically assess microglial activation in BA24 white matter of depressed suicides and matched controls. Post-mortem BA24 samples from 26 depressed suicides and 23 sudden-death controls were obtained from the Douglas Brain Bank. Expression levels of the microglial marker IBA1 were measured by qRT- PCR. The different stages of microglial activation were assessed in IBA1-immunostained sections by combining three-dimensional cell reconstructions and a semi-stereological approach, using the Neurolucida and Stereoinvestigator softwares, respectively. IBA1 mRNA levels were significantly increased in the white matter of depressed suicides when compared to controls (p=0.0042). Furthermore, our morphological analyses revealed a higher primed/resting microglial ratio (p=0.031) in the same area. Increased mRNA IBA1 expression, together with a greater proportion of primed/resting microglia in BA24 white matter of depressed suicides suggest the presence of microglial reactivity in this limbic brain region, in accordance with our previous findings and in support of the neuroinflammatory hypothesis of depression.

2-B-38 Glycine priming is regulated by exon 5 in GluN1 splice variants of NMDARs

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NMDARs are a principal subtype of excitatory ligand-gated channels with prominent roles in the CNS. Previously, we discovered that glycine stimulation independent of glutamate initiates transmembrane signalling, priming the NMDARs for endocytosis. Recently, we demonstrated that activation of the glycine site directly leads to recruitment of adaptin â2 (AP2) to recombinant NMDARs containing GluN1-1a. Three exons in

GRIN1 undergo RNA splicing to produce eight GluN1 variants. Thus, we examined the effect of glycine stimulation on AP2 recruitment among these variants. We found the presence of exons 21 or 22, which encode C1, C2, C2' cassettes in the GluN1 C terminal, had no effect on glycine-primed internalization of exon 5 (N1) lacking NMDARs. However, all N1 containing receptors systematically showed no glycine-stimulated internalization. Next, we found that glycine stimulation increased AP2 association with GluN1-1a containing NMDARs, but no enhanced AP2 association was observed with receptors containing GluN1-1b. Moreover, glycine stimulation did not cause a progressive reduction in NMDAR-mediated current in cells expressing GluN1-1b subunits nor surface NMDAR endocytosis. Therefore, our results indicate that differences in glycine priming among NMDAR splice variants also regulate receptor internalization. It is known that the different GluN1 splice variants can interact with different binding partners and that these interactions can tightly regulate GluN1 subunit trafficking. Thus, suggesting there may be unique roles for GluN1 splice variants in synaptic transmission.

2-B-39 Hypofunction of prefrontal 5-HT1A receptors in a genetic mouse model of depression

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Serotonin (5-HT) receptors in the prefrontal cortex are thought to play a major role in the pathology of depression. Yet, it remains unclear how the function of these prefrontal 5-HT receptors might be altered in depressive states. Here, we use whole-cell electrophysiological recordings in acute prefrontal brain slices to examine the 5-HT receptor currents in a genetic mouse model of depression, mice heterozygous for deletion of the serotonin transporter (5-HTT /-). We observed a significant increase in the inhibitory, outward currents elicited by 5-HT in the adult prefrontal cortex of 5-HTT /- mice, as compared to littermate wildtype controls. Pharmacological experiments revealed that the 5-HT1A receptors are the primary mediator of the 5-HT outward current in both 5-HTT /- mice and their wildtype siblings. Notably, acute blockade of the presynaptic 5-HTT activity with either fluoxetine or citalopram did not increase 5-HT-elicited currents in wildtype mice, suggesting that the electrophysiological differences in the 5-HTT /- mice results from alterations to the postsynaptic 5-HT1A receptors themselves, their G protein coupling, or their downstream channel mediators. Together, our findings indicate that increased 5-HT1A inhibition represents a source of long-term neuronal dysfunction in 5-HTT /- mice. Similar pathophysiology in humans would be expected to result in the cortical hypofunction observed in patients suffering from depression.

2-B-40 Expression of an N-terminal TRPV1 variant cloned from mouse supraoptic nucleus confers osmosensitivity on heterologous cells and hypothalamic neurons from TRPV1 knockout mice

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Hypothalamic osmosensory neurons are depolarized and excited by hypertonicity, a response mediated in part by the activation of ruthenium red sensitive cation channels during cell shrinking. Recent studies have indicated that a channel encoded as an N-terminal variant of TRPV1 may be responsible for this effect in supraoptic nucleus (SON) neurons, but the structural identity of this variant remains unknown. Here, we cloned a TRPV1 variant isolated from mouse SON. This variant lacks exons 1-4 of TRPV1 and produces a channel lacking a large part of the N-terminus. Single cell RT-PCR analysis indicated that neurons in the SON specifically express this transcript, but not full length TRPV1. Voltage clamp analysis showed that a proportion of HEK cells transfected with this variant (but not full length TRPV1 or mock controls) generate sustained and dose-dependent inward currents when challenged with hyperosmotic media (comprising excess mannitol). Similar responses were evoked when cell volume was reduced by the

application of negative pressure to the patch pipette, and both types of responses were blocked by ruthenium red. Moreover, depolarizing responses and increased action potential firing frequency could be induced by modest hypertonicity (20 mosmol/kg) in a high proportion of cultured hypothalamic neurons obtained from TRPV1 K.O. mice when the cells had been transfected with the TRPV1 variant channel, but not in untransfected neurons. These results provide strong support for the involvement of an N-terminal variant as the hypothalamic osmoreceptor.

2-B-41 A Potential Role for Postsynaptic Pannexin-1 in Regulating Pre-Synaptic Glutamate Release

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Synaptic plasticity is a change in synaptic strength between two neurons due to a change in receptor number in the postsynaptic membrane, or a change in the release probability of neurotransmitter. Changes in synaptic strength are readily seen in the CA1 region of the hippocampus as long-term potentiation (LTP) and long- term depression of synaptic events. Pannexin-1 (Panx1) channels conduct ions and molecules, including calcium, and therefore may play a role in synaptic plasticity. To test this, we used whole-cell patch clamp recordings from acute hippocampal brain slices and applied a Panx1 blocking antibody to the intracellular solution. A marked increase in the frequency, but not amplitude, of spontaneous excitatory postsynaptic currents (sEPSC) was observed, suggesting enhanced presynaptic release of glutamate. Synthesis of an interfering peptide that targeted the antibody's epitope in the c-terminal of Panx1 increased sEPSC frequency when applied through the patch pipette. Interestingly, bath application of pannexin inhibitors failed to affect sEPSCs and Panx1 block did not alter high frequency synaptic stimulation induced LTP. This suggests that Panx1 is important for release of a retrograde messenger that acts at the presynaptic membrane to alter release probability. We tested if there was a role for endocannabinoids using electrophysiological techniques, but no effect on sEPSCs was found. While the identity of the retrograde messenger remains unknown, our data suggest that protein-protein interactions at the Panx1 c-terminus may be critical for its release.

2-B-42 Synaptic GABAA receptors are inhibited by interleukin-1beta through phosphoinositide 3-kinase pathway

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Gamma-aminobutyric acid (GABA) type A receptors (GABAARs) are broadly divided into two major groups. Synaptic GABAARs generate transient inhibitory postsynaptic currents (IPSCs), and extrasynaptic GABAARs generate a persistent, tonic inhibitory conductance. We show that a tonic conductance in hippocampal neurons is enhanced by a pro-inflammatory cytokine interleukin-1beta (IL-1beta) via a p38 MAP kinase pathway, whereas the miniature IPSCs (mIPSCs) are inhibited by IL-1 beta (Wang et al, Cell Reports, 2012). The goal of this study is to identify the cytosolic factors that cause the divergent effects The effects of IL-1beta on GABA-evoked currents and mIPSCs were investigated by using whole-cell voltage clamp recording technique in cultured murine hippocampal neurons. IL-1beta (20 ng/ml) inhibited currents activated by GABA (1-10 μM), and this effect is mediated by IL-1 receptor because IL-1 receptor antagonist blocked the inhibitory effect of IL-1beta. Furthermore, phosphoinositide 3-kinase (PI3K) contributes to the inhibitory effect of IL-1beta on GABA-evoked currents, since PI3K inhibitors LY294002 and wortmanin (but not a p38 MAP kinase inhibitor) abolished such an effect. IL-1beta also inhibited the amplitude (but not frequency) of mIPSCs, and this effect was blocked by PI3K inhibitors. Therefore, IL-1beta-mediated inhibition of synaptic GABAARs is through PI3K. Future studies will address the functional significance of the homeostatic regulation of

synaptic (decrease) and extrysynaptic (increase) GABAARs by IL-1beta.

2-B-43 Glial gap junction interactions are preserved in detergent-solubilized membranes

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Communication between glial cells is accomplished through cell-cell coupling provided by gap junction channels composed of connexin proteins. Connexins hexamerize to form single membrane channels, or gap junction channels, wherein closely apposed single membrane channels dock to allow cytoplasmic continuity amongst coupled cells. Such gap junctional communication enables formation of the glial syncytium. It is established that oligodendrocytes express Cx32, Cx29, and Cx47, while astrocytes express Cx43, Cx30, and Cx26. It is also understood that functional heterotypic gap junctions between oligodendrocytes and astrocytes are made through Cx32:Cx30, and Cx47:Cx43 channels. Co-localization of these connexins has been confirmed by confocal imaging, while functional networks have been explored via dye transfer studies in acute brain slices of connexin-null animals. Here, I present a third line of novel biochemical evidence that Cx32:Cx30 gap junction channels exist amongst coupled oligodendrocytes and astrocytes. In detergent-solubilized protein lysates from whole murine brain tissue, we show that oligodendrocytic Cx32 is immunopurified with the apposing astrocytic Cx30 connexon. This interaction is specific since Cx32 does not immunopurify with oligodendrocytic Cx47 (oligodendrocytes dock only through homotypic Cx32:Cx32 or Cx47:Cx47 pairings), or other cellular proteins tested in our screens. These data show that extracellular gap junctional interactions are preserved in detergent-solubilized membranes, and help solidify our knowledge of functional glial channel pairings.

2-B-44 Activation of Thalamic δ-Subunit Containing GABAa Receptors Promotes Cortical Deactivation

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Augmentation of γ-aminobutyric acid (GABA)-ergic neural activity promotes natural sleep. Many anesthetics enhance neural inhibition via interactions with binding sites on δ-subunit-containing GABAa receptors (δGABAaR). The thalamus is a key structure controlling brain arousal. Activation of δGABAaR in the ventral basal complex (VB) of the thalamus elicits a tonic hyperpolarization in vitro that promotes a change in neural population activity consistent with brain deactivation. We examined the influence of δGABAaR activity in the VB on cortical activity. Experiments were conducted in 25 freely behaving δGABAaR knockout (Gabrd-/-) and wild type (WT) mice. Electrocortical activity was recorded during bilateral microperfusion of artificial cerebrospinal fluid (aCSF), 10μM and 50μM THIP (a δGABAaR-preferring agonist) into the VB. Mice of each genotype also served as time-controls, receiving only aCSF. In WT mice, 50μM THIP at the VB increased 1-4Hz electrocortical activity in non-rapid eye movement (NREM) sleep and waking (13±6%, 21±7%, respectively; $p<0.05$). Transitions into NREM and REM sleep also occurred more rapidly (17±5 %, 31±10%; $p<0.05$). Sigma power (10-15Hz) and spindle density (7-14Hz) during NREM sleep were also reduced (10±6%, 29±15%; $p<0.05$). Importantly, no such changes occurred with THIP in Gabrd-/- and WT time-control mice. Since prominent delta oscillations are a hallmark of sleep and anesthetic states, these data suggest that δGABAaR at the VB promote cortical deactivation, and as such are positioned to contribute to the induction of sleep and sedation.

2-B-45 Hydrogen peroxide increases tonic GABA current in hippocampal neurons

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Background: Oxidative stress, which produces hydrogen peroxide (H2O2), causes memory impairment through poorly understood mechanisms. We previously showed that a tonic inhibitory conductance generated by GABAA receptors regulate learning and memory in mice. The goal of this study was to determine whether H2O2 modulates the tonic inhibitory conductance in hippocampal neurons. Methods: Primary cultures of hippocampal neurons were prepared from embryonic mice. Whole-cell recordings studied the effects of H2O2 (200 µM) on GABA-evoked currents that were generated by applying GABA (0.3 to 100 µM) for 20 s, or by prolonged bath applications of GABA (0.5 µM), where the amplitude of the "tonic" current was assessed by co-applying a GABAA receptor antagonist (bicuculline) and measuring the change in holding current. Results: H2O2 caused a 3-fold increase in the amplitude of the GABA-evoked current, but only for current activated by low concentrations of GABA (0.3 to 1 µM). The tonic current was increased 2-fold by H2O2. The effects of H2O2 were concentration-dependent and persisted after washoutof H2O2. Discussion: These results provide the first evidence that H2O2 robustly increases the tonic inhibitory conductance in hippocampal neurons and suggest a molecular mechanism by oxidative stress causes memory impairment.

2-B-46 Podosomes in microglia: Ca2+-regulated multi-molecular structures for adhesion, ECM degradation and migration

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Microglia must migrate through dense neuropil and extracellular matrix (ECM) during development and to reach damaged sites in the injured or diseased CNS. It is not known how they do it. We recently discovered that migrating microglia contain large numbers of podosomes that self-organize into a large ring ('podonut') in the lamellum at the leading end, and they degraded ECM. Podosomes are tiny multi-molecular structures (<1 µm) with an F-actin-rich core surrounded by a ring of adhesion and structural proteins. They are thought to promote and regulate molecular signals for cell adhesion and ECM degradation. We labeled microglia podosomes using components of the core (F-actin, Arp2/3) and ring (talin, vinculin), and then identified Tks5, phosphorylated caveolin-1 and Nox1 as prominent components. Finely tuned Ca2 signaling is important for cell migration, adhesion and contraction of the actomyosin network. Surprisingly, we discovered that microglial podosomes contain two ion channels (Orai1/CRAC; Ca2 -activated SK3), and their accessory molecules (STIM1, calmodulin), and that podosome formation and microglial migration require Ca2 entry through Orai1/CRAC channels. CRAC and SK3 were both needed for effective invasion through ECM. The discovery of functional podosomes in microglia has broad implications. Migration of these innate immune cells is crucial in CNS development, after damage, and in diseases involving inflammation and matrix remodeling. These complex podosome structures might account for their ability to adhere to and degrade the ECM for efficient migration.

2-B-47 Hyperpolarization-activated current (Ih) is reduced in hippocampal neurons from mice lacking α5GABAA receptors

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The expression of γ-aminobutyric acid type A (GABAA) receptors can both drive and mediate homeostatic changes in neuronal function. Such a homeostatic relationship was recently described between α5 subunit-containing GABAA (α5GABAA) receptors which generate a tonic inhibitory conductance, and HCN channels which generate the hyperpolarization-activated cation current (Ih) in HCN1 null-mutant mice. Specifically, deletion of HCN1 induced a reciprocal increase in the tonic current generated by α5GABAA receptors in cortical neurons resulting in the preservation of

dendritosomatic synaptic function. Here, we report that mice lacking the α5 subunit gene (Gabra5-/-) exhibit reduced Ih and HCN1 protein in hippocampal neurons. Compared to WT, Ih was lower in pyramidal neurons from Gabra5-/- mice in both cultured neurons (40% lower) and in acute brain slices (28% lower). The resting membrane potential was similar in WT and Gabra5−/− neurons, but Gabra5−/− neurons exhibited reduced membrane hyperpolarization after trains of action potentials, and an increase in frequency-dependent membrane impedance. The expression levels of HCN1 protein was 41% lower in the hippocampus of adult Gabra5−/− mice. Collectively, these data indicate that loss of a tonic GABAergic inhibitory conductance was followed by a compensatory reduction in Ih. The results further suggest that the maintenance of resting membrane potential is preferentially maintained in mature and immature hippocampal neurons through the homeostatic co-regulation of structurally and biophysically distinct cation and anion channels.

2-B-48 Subcellular Targeting of Glutamate Receptor Subtypes During Homeostatic Synaptic Plasticity

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The rules governing the targeting and trafficking of AMPA and NMDA glutamate receptors during rapid Hebbian forms of synaptic plasticity have been well characterized, but those that are operant during homeostatic forms of synaptic plasticity (HSP) are less well understood. Here, we investigated the subunit-specific regulation of AMPA and NMDARs in CA1 pyramidal neurons during TTX-induced HSP in organotypic hippocampal slice cultures. We provide biochemical, pharmacological and biophysical evidence indicating that HSP at Schaffer-Collateral synapses involves the insertion of calcium-permeable GluA2-lacking AMPARs, and triggers a switch from GluN2B- to GluN2A-containing NMDARs. We then asked whether these specific glutamate receptor subtypes were differentially targeted to subcellular compartments during HSP. We thus combined electrophysiological recordings with 2-photon imaging and glutamate uncaging and found that whereas GluA2-lacking AMPARs were readily detected on both spines and extrasynaptic regions of dendrites, GluN2A-containing NMDARs were selectively targeted to spines. These data outline a striking differential targeting of AMPA and NMDAR subtypes during HSP. Notably by documenting a homeostatic switch in NMDAR subunit composition, these results expand the repertoire of the cellular processes engaged by central neurons during HSP. Future investigations will be necessary to fully appreciate the functional consequences of these specific targeting behaviours on plasticity rules and synaptic computation.

2-B-49 Synaptic vesicles expressing adaptor protein 3 contribute primarily to asynchronous release and regulate the fidelity of neurotransmission at hippocampal mossy fibre terminals

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Endocytosis is an important step in the synaptic vesicle recycling; it helps to maintain reliable neurotransmitter release. Two major pathways of endocytosis co-exist in the same presynaptic terminal: clathrin-dependent endocytosis of single vesicles utilizing adaptor protein AP-2 and bulk endocytosis leading to the formation of endosomes and dependent on adaptor protein AP-3. Vesicles derived in these two pathways differ in their molecular content and represent distinct vesicular pools. We used AP-3 knockout mice (Ap3b2-/-) lacking endosomal vesicle formation to explore physiological role of the vesicular pool formed via this pathway in synapses between mossy fiber boutons and hippocampal CA3 pyramidal cell. Spontaneous and evoked EPSCs had similar amplitude and kinetic properties, moreover quantal parameters (p, Q and N), ready releasable pool size and its recovery speed were comparable between WT and KO mice. However, in KOs decay time

constant of release was significantly faster (3.7 ± 0.4 ms vs 5 ±0.4 ms) and was accompanied with reduced asynchronous release (3.8 vs 7.4 Hz). In addition, stimulation with natural spike trains revealed significantly reduced probability of postsynaptic APs and increased variability of the responses. Our data suggest that vesicles generated via bulk endocytosis contribute primarily to asynchronous release. The lack of asynchronous release renders information transfer from granule cells to hippocampal pyramidal cells less reliable, and therefore it could influence spatial memory.

2-B-50 Increased activity of alpha5GABAARs contributes to post-anesthetic memory deficits

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General anesthetics cause memory deficits that persist long after the anesthetic has been eliminated. We previously showed that pharmacologically inhibiting γ-aminobutyric acid type A receptors that contain the alpha5 subunit (a5GABAAR) both prevented and reversed memory deficits after anesthesia in mice (Anesthesiology 2010: 113 (5): 1061-71, Anes Analg 2012: 114 (4): 843-55). Here, we tested the hypothesis that a5GABAARs are necessary for the development of anesthetic-induced memory deficits and that the activity of these receptors is enhanced after anesthesia. Wild-type (WT) and a5GABAAR null-mutant (Gabra5-/-) mice were treated with the intravenous anesthetic etomidate (8 mg/kg i.p.). Memory was assessed 24 h, 72 h and 1 week later with the object recognition task. Also, mice were treated with etomidate and hippocampal slices were prepared 24 h later. Long-term plasticity was studied in the CA1 region after 20 Hz stimulation of Schaffer collaterals. The amplitude of a tonic inhibitory conductance generated by a5GABAARs was measured in CA1 pyramidal neurons in brain slices using whole cell recording methods. The results showed that WT but not Gabra5–/– mice exhibited impaired recognition memory for at least 72 h after etomidate. In preliminary studies, long-term potentiation was reduced in brain slices from etomidate-treated WT mice and the amplitude of the tonic conductance was increased. Collectively these results suggest that a5GABAARs are necessary for post-anesthetic memory deficits and these deficits may be caused by an increase in the activity of a5GABAARs.

C – Disorders of the Nervous System

2-C-51 Virtual Reality as a Potential Rehabilitation Tool in Parkinson disease

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Background: Augmented immersion virtual reality (AIVR) offers flexibility for designing rehabilitation tasks. The role of context in motor performance in persons with Parkinson disease (PwPD) suggests value in exploring the use of AIVR in this population. Objective: Use AIVR in a cohort of PwPD and controls to determine: 1) Does motor performance of PwPD differ between real-world (RW) and AIVR tasks? 2) Is this effect different in PwPD versus controls? Method: Seventeen PwPD (11 male; Mean age 67.2 ± 4.7 years, Mean disease duration 6.0 ± 3.3 years) and 9 controls (5 male; Mean age 63.1 ± 4.9 years) completed functionally relevant motor tasks in three AIVR scenarios: 1) Watering plants in a living room, 2) Placing items in baskets at a grocery store, and 3) Crossing a street with time constraints. Comparable RW motor tasks were also performed. Participants completed the weekly protocol for 3 weeks Results: There was an effect of group ($F(2,143) = 11.73$, $p = .000$, $ç2p = .14$) on range of motion in the plant watering tasks. There was an effect of group ($F(2,143) = 7.1$, $p = .001$) and environment (AIVR vs RW) ($F(2,143) = 14.86$, $p = .000$) on accuracy and time in the grocery store task. There was an effect of visit number ($F(10,280) = 1.89$, $p = .007$), group ($F(5,140) = 3.15$, $p = .010$), and environment ($F(5,140) = 4.57$, $p = .000$) on speed and accuracy in the street crossing task. Conclusions: An AIVR program was

developed to simulate three scenes. Differences in performance between the AIVR and RW environments may be due to altered delivery of sensory information.

2-C-52 Mechanisms of increased tau phosphorylation during aging

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Alzheimer's disease (AD) has many risk factors. Only a small proportion of AD is due to genetic mutations inducing early onset AD, whereas the large majority of cases is of late onset and sporadic in origin. Aging is considered to be the most important risk factor for late-onset sporadic AD. The histopathological hallmarks of Alzheimer's disease include neurofibrillary tangles (NFT), composed of abnormally hyperphosphorylated tau protein assembled in paired helical filaments (PHF). Our experiments are oriented towards understanding the impact of aging on tau phosphorylation and its mechanisms. The hypothesis is that aging will induce the gradual building of hyperphosphorylated tau, and that tau phosphorylation will be mediated by deregulation of kinases (e.g. GSK-3β) or phosphatases (e.g. PP2A) consequent to dysfunction in insulin signaling pathway. To assess this, two lineages of mice were used: WT and 3xTg-AD. Both were represented in five different age groups: 3, 6, 12, 18 and 24 months. Cortexes were extracted and then analyzed for levels of tau phosphorylation through the Western Blot technique. Early results suggest an increase of tau phosphorylation with age in both groups, although more drastically in the 3xTg-AD genotype. This goes in the same direction of our hypothesis.

2-C-53 Quantification of amyloid-beta load and cell differentiation following transcranial focused ultrasound in a mouse model of Alzheimers disease

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During the progression of Alzheimers disease (AD), individuals develop neuropathologies that contribute to cognitive impairments related to learning and memory. These pathologies include accumulation of toxic amyloid-beta peptides (Aß), which play a role in inducing the degeneration of healthy neurons. Previously, our group used MRI-guided focused ultrasound (MRIgFUS) to locally and transiently increase the permeability of the blood-brain barrier, allowing delivery of anti-Aß antibodies to the brain in a mouse model of AD. As a result, it was found that Aß plaque number and size were significantly reduced by 4 days post-treatment (Jordão et al., 2010). Further studies by our group demonstrated that MRIgFUS alone could significantly reduce Aß plaque size by 4 days post-treatment (Jordão et al., in revision). Here, we examine the long-term effects of MRIgFUS on Aß plaque load and cell differentiation. Immunohistochemistry, stereology and confocal microscopy were used to quantify these effects in the hippocampus at 2 weeks following MRIgFUS therapy. Preliminary results indicated that Aß plaque number and size were not significantly different following MRIgFUS treatment with or without anti-Aß antibodies at 2 weeks post-treatment. We are evaluating MRIgFUS effects on cell differentiation using immunohistochemistry and confocal microscopy. Overall, these results demonstrate that a single MRIgFUS treatment is not sufficient to keep Aß load reduced for 2 weeks after treatment, suggesting that additional interventions are required to minimize AD neuropathologies long term.

2-C-54 Characterization of hypo-frontal electrophysiological activities in hRNGF rat model of schizophrenia

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Background: A histological study on the hRNGF rat model shows that partial ablation of subplate and GABAergic synaptic abnormalities of the pre-frontal cortex (PFC) are responsible in altering dopaminergic (DA) activity. Although their finding showed the histological and behavioral similarities between hrNGF model and schizophrenia, electrophysiological properties of this model have not been adequately studied. Method: Using in vivo tetrodes recording in control and hRNGF model, a data-driven nonlinear oscillator model has been developed to show the mechanism of stochastic resonance in terms of explaining inhibitory and excitatory neuronal activities in PFC. In order to explain the correlation of an over inhibited state with evidence of excessive GABAergic activity, these models are perturbed in presence of 'amphetamine'. Results: Increase GABAergic synaptic abnormalities and loss of dopamine fiber densities in hRNGF model may reduce DA neuronal activities in PFC. These altered DA activities in disease state can be quantified in terms of reduced spontaneous activity of neurons in PFC, which may show inability of symmetry breaking bistable dynamic states in presence of excitatory perturbation. These may help to characterize dopamine agonist and/or antagonist activities in our bistable oscillator model and to demonstrate inability to retrieve information flow in hRNGF model. Conclusion: The reduced stochastic resonance in dynamic phase space and its relation to GABAergic synaptic abnormalities in disease state may represent hypofrontality in the hRNGF rat model.

2-C-55 Scyllo-Inositol As A Potential Therapeutic Agent For Angelman Syndrome

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Angelman syndrome (AS) is a debilitating genetic neurodevelopmental disorder caused by mutations or deletions of the maternally inherited Ube3a gene. Ube3a gene encodes a HECT (homologous to E6-associated protein C terminus) domain E3 ubiquitin ligase involved in the protein degradation pathway; a mutation of which impairs the function of the ubiquitin-proteasome pathway (UPP). scyllo-Inositol (SI) is an endogenous inositol stereoisomer shown to inhibit amyloid-β fibril assembly and improve disease pathology in Alzheimer's disease by restoring proteostasis. The similarities between the pathologies arising from impaired protein degradation and altered proteostasis led us to hypothesize that changes in the UPP is likely to alter the activity of the autophagy- lysosomal degradation system and treatment with SI will reverse these pathological manifestations. We examined autophagal activity using the phosphorylation state of the mTOR-specific substrate p70s6kinase as a measure of mTor activity, and the protein levels of the autophagy markers LC3, Cathepsins B and D. We also investigated proteosomal function using the trypsin and chymotrypsin like activities of the 26S proteosome. We demonstrated a scyllo-inositol effect in both pathways in the maternally inherited TgUbe3a mice. These data provide a potential intervention to restore proteostasis in an AS model.

2-C-56 Chemical genetic screens of TARDBP modifiers in C. elegans and zebrafish

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The DNA/RNA-binding protein TDP-43 is found in protein aggregates in numerous neuropathies, including Amyotrophic Lateral Sclerosis (ALS) and related dementia, but little is known about the neurotoxic mechanisms. We have generated C. elegans and zebrafish models expressing wild-type or mutant human TDP-43[G348C] that reflect aspects of ALS. To explore the potential of our models in identifying chemical suppressors of mutant TDP-43 neuronal toxicity, we tested a set of

compounds with potential neuroprotective properties. We identified methylene blue, salubrinal, guanabenz and phenazine as potent suppressors of TDP-43 toxicity in both our models. Next, we found that in our models all four compounds corrected motor deficits and reduced the level of oxidative stress associated with the expression of mutant proteins. Using C. elegans genetics we show that these compounds reduced protein misfolding as detected by induction of hsp-4::GFP expression that was suppressed by mutations in either ire-1 or xbp-1 in the unfolded protein response (UPR) pathway. As oxidative stress is a convergent outcome of the UPR and ER stress pathways, we tested for activation of the ER oxidoreductase enzyme ero-1 and observed a reduced activation by mutation of TARDBP in our models. Our results indicate these compounds can rescue toxic phenotypes associated with mutant TDP-43 by reducing oxidative stress leading to neuronal dysfunction. Our data also indicate that protein folding homeostasis in the ER may be an important target for therapeutic development in ALS and other neurodegenerative diseases.

2-C-57 Sleep-wake cycle alterations at early and advanced pathological stages in the TgCRND8 mouse model of Alzheimer's disease

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Individuals affected by Alzheimer's disease (AD) experience a progressive decline in cognitive function eventually leading to a debilitating loss of memory, reasoning and communication. Although AD is readily associated with such cognitive symptoms, patients can also experience important neuropsychiatric symptoms, including perturbations of sleep-wake cycle patterns (Lyketsos et al., 2011). Features of sleep-wake cycle disturbances in human AD include a decrease in non-rapid eye movement sleep (NREMS) and rapid eye movement sleep (REMS) as well as changes in the electroencephalogram power spectrum (Jeong, 2004, Weldemichael et al., 2010). To determine if the TgCRND8 mouse model of amyloidosis mimics sleep-wake pattern alterations observed in human AD, polysomnographic recordings were performed and the vigilance state durations over the light and dark cycle of 3, 7, and 11-month-old TgCRND8 mice were measured. During the active phase, at all ages studied, TgCRND8 mice spent a significantly greater amount of time awake and a significantly lower amount of time in NREMS and REMS when compared to controls. During the resting phase, 3, 7 and 11-month-old TgCRND8 spent a significantly lower amount of time in NREMS and a significantly greater amount of time awake than controls. Differences in REMS during the resting phase only emerged at 11 months of age, where TgCRND8 mice spent a significantly lower amount of time in REMS. We acknowledge support from Dr. John Breitner of the StoP-AD centre at the Douglas Mental Health University Institute and from CIHR to AA and RQ.

2-C-58 Nicotine Enhances Both Sign-Tracking Behavior and Responding for Conditioned Reinforcement

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Nicotine reinforcement is thought to be, at least in part, due to an effect on enhancing the attractive and motivating properties of other, non-nicotinic reward stimuli. Our lab and others have shown that nicotine facilitates approach to a reward delivery receptacle in the presence of a conditioned stimulus (CS) during Pavlovian association trials, but this latter effect is not always observed. This may be due to differences in conditioned response trajectories under the influence of nicotine, with some animals attracted toward the CS itself rather than the goal receptacle. 40 water-restricted rats received nicotine (n = 20) or saline (n = 20) injections prior to 6 daily Pavlovian autoshaping trials, where an illuminated lever-CS was inserted into the test chamber just prior to the delivery of a water reinforcer. Animals that received nicotine exhibited higher levels of conditioned responding directed toward the lever-CS. Next, a subgroup of

nicotine-exposed (n = 10) and saline-exposed (n = 10) animals were switched to saline or nicotine pretreatments for 6 additional trials. Removing nicotine decreased responding on the lever. Responding in the water receptacle was unaffected by nicotine. In a test of the motivating properties of the lever-CS, presentations of the lever supported the acquisition of a new operant response and nicotine enhanced this effect in animals with a history of nicotine exposure. Together, these data suggest that nicotine reinforcement is dually influenced by effects on enhancing both the attractive and motivating properties of CSs.

2-C-59 Dysfunction of voltage-gated Na+ channel conductance and excitatory synaptic activity in MECP2e1- mutant patient induced pluripotent stem cell-derived neurons

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Rett syndrome (RTT) is principally caused by mutations in Methyl CpG-binding protein 2 gene (MECP2), and MECP2 has two isoforms, MECP2e1 and MECP2e2. MECP2e1 is more highly expressed in the brain than MECP2e2 and mutations of MECP2e1 alone can lead to neurological phenotypes in RTT. The pathophysiological mechanisms underlying RTT phenotypes caused by MECP2e1 mutations remain unknown. We performed patch-clamp recordings in normal and MECP2e1-mutant human induced pluripotent stem cell (hiPSC)-derived neurons to investigate cellular basis leading to RTT phenotypes. Normal and mutant cells had functional neuronal properties, generating tetrodotoxin-sensitive, sodium channel-mediated spontaneous and/or evoked action potentials (APs) and displaying spontaneous synaptic activity. Statistical analysis revealed that mutant neurons had higher input resistance and exhibited decreased numbers of APs evoked by injecting depolarizing currents. Evoked APs in mutant neurons also had smaller amplitude (42.7 ± 3.5 versus 51.6 ± 2.8 pA; P< 0.05) and prolonged half-duration (11.5 ± 1.9 versus 5.8 ± 0.9 ms; P< 0.01). The defects may be attributed to a significant decrease in voltage-gated sodium currents (-0.8 ± 0.1 versus -1.1 ± 0.1 nA, P<0.05) in mutant neurons. Furthermore, mutant neurons had dysfunctional synaptic activity with decreases in both frequency and amplitude of mEPSC. This is the first evidence demonstrating dysfunction of sodium channels and synaptic activity in hiPSC-derived neurons with specific mutations in MECP2e1 and such defects may lead to RTT phenotypes.

2-C-60 NMDA-receptor activation but not ion flux is required for amyloid-beta to induce synaptic depression in CA1 pyramidal neurons

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Introduction: Alzheimer disease (AD) is the most common neurodegenerative disorder of modern society. It affects the elderly and causes impaired memory formation and loss of higher cognitive functions. Biologically, the disease is characterized by a gradual decrease of synaptic function and neuronal loss. There is considerable evidence supporting the involvement of oligomeric amyloid-beta (Aβ) in the etiology of AD. Historically, however, AD research has mainly focused on the long-term changes caused by Aβ rather than analyzing its immediate effects. Methods: In this study we used hippocampal slice cultures prepared from 7 days old rats and maintained them in culture for 5 to 7 days. Neuronal activity was recorded with field and whole-cell patch clamp techniques; AMPA/NMDA-receptor dependent synaptic responses were measured by stimulating the Schaffer collaterals. Results: In this study we show that acute perfusion of hippocampal slice cultures with oligomeric Aβ depresses synaptic transmission on CA1 pyramidal neurons within 15 minutes. This depression is dependent on synaptic stimulation and can be blocked by application of APV and Ifenprodil (NMDA-receptor antagonists), but not by application of MK-801 (NMDA-receptor channel blocker). Conclusions: Our study suggests that Aβ

dependent synaptic depression is mediated through a use-dependent metabotropic-like mechanism of the NMDA-receptor, i.e. it is not dependent on ion flux through the NMDA-receptor.

2-C-61 Identification of novel connexin modulators for potential therapeutic use following neural injury

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The connexin family comprises 21 proteins in humans representing the structural units of intercellular gap junction channels. These channels provide a means for cells to exchange small metabolites and signaling molecules with adjacent cells though gap junctions or, when inserted into non-junctional membranes, to pass molecules to and from the extracellular space (hemichannels). Compelling evidence implicates connexin-mediated cell-cell communication in the control of neural progenitor cell proliferation, survival, and migration. Moreover, the dysregulation of connexin function and expression that results from insults to the central nervous system has been shown to further contribute to the secondary expansion of lesions in the days and weeks after the initial insult. While these data suggest that connexins represent a novel therapeutic target with potential to both 1) reduce the extent of neural injury and 2) promote neural repair and regeneration, we currently lack the necessary repertoire of therapeutically useful connexin-specific modulators to test these hypotheses. We present here the results of a series of functional and expression screens exploring a rare collection of phenolics, alkaloids, terpenes, ethnobotanical extracts, and natural products for compounds that differentially alter connexin expression, metabolic gap junction coupling and/or hemichannel function. Together, these screens have identified a number of novel connexin-altering compounds that exhibit minimal to no toxicity in vitro at effective concentrations.

2-C-62 Evaluation of the neuroprotective effects of Rhodiola rosea L. (Crassulaceae) in the TgCRND8 mouse model of Alzheimer disease

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Rhodiola rosea L. is a widely used medicinal plant in the sub-Arctic regions of Eurasia. It was traditionally used to improve memory and concentration, alleviate depression and enhance mental performance under stress. In Canada, the Inuit in Nunavik, Québec use R. rosea to boost mental and physical well-being. Extracts of Nunavik R. rosea show anxiolytic activity in rats, indicating the potential of bioactive phytochemicals to cross the blood-brain barrier, and providing preliminary evidence of activity in the context of neurological disorders. Here, we assessed the neuroprotective effects of R. rosea in the context of Alzheimer disease (AD), characterized by progressive loss of memory in addition to other neuropsychiatric symptoms, using the TgCRND8 mouse model. R. rosea extract was administered orally to male and female mice, wild-type and transgenic, for eight weeks at 100 mg/kg body weight. Males were subjected to the Morris water maze test for assessment of spatial learning and memory. Reduced mortality of R. rosea-treated transgenic males led us to explore mechanism of action by examination of cerebrovascular pathology using immunofluorescence techniques. Females were used to assess changes in the levels of glycerophosphocholine lipids in the hippocampus and temporal cortex, which play a key role in signalling transition from pre-symptomatic to symptomatic AD-like impairment. This work highlights the importance of treatment of mental health disorders in traditional medicine and the need to validate the activity of natural products in relevant pre-clinical settings.

2-C-63 Dysfunctional BDNF/TrkB/PI3K signaling in autism disrupts intracellular pathways regulating spine protein synthesis and spine dynamics

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Abnormalities in spines, leading to synaptic dysfunction and perturbed neuronal circuit development, may account for cognitive and behavioural deficits of autistic patients. Spine protein synthesis and dynamics are regulated by intracellular signaling cascades triggered by BDNF/TrkB-mediated activation of PI3K. We previously demonstrated down-regulation of the BDNF/TrkB signaling pathway in fusiform gyrus of autism versus controls samples. We now aimed to investigate whether BDNF/TrkB-activated intracellular cascades, PI3K-Akt-mTOR, involved in spine protein synthesis, and PI3K-Eps8-Rac, regulating synapse formation, are disrupted in autism. We examined the mTOR effector p70S6K and the PI3K-activated signaling molecule Eps8. We also assayed protein expression of Erk1/2, SNAP-25 and p75NTR, which affect different pathways involved in spine dynamics and function. Protein was examined by Western blotting in postmortem fusiform gyrus of autism and control subjects. Significantly decreased p70S6K and Eps8 protein levels were found in fusiform gyrus of autistic subjects versus controls. No significant difference in Erk1/2 or SNAP-25 protein expression was measured. Lastly, a trend towards increased p75NTR receptor was observed. Both reduced p70S6K and Eps8 protein levels are consistent with down-regulation of the BDNF/TrkB signaling pathway. The trend towards elevated p75NTR receptor in autism is consistent with increased proBDNF protein that we observed in autism. These abnormalities may affect regulation of spine dynamics and density and lead to synaptic dysfunction in autism.

2-C-64 Differential effect of NMDA receptor antagonism on dendritic spine density

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Current clinical trials are investigating the effect of ketamine, an NMDA receptor antagonist, as an antidepressant. Early studies indicate that ketamine has a rapid onset of action and sustained antidepressant effects after a single infusion; however, ketamine has psychotomimetic effects and the long-term effects of ketamine on the brain are unknown. One study determined that the antidepressant effects of ketamine are due to an increase in dendritic spine density in the cortex of rats. On the other hand, our laboratory demonstrated that chronic treatment with MK-801, another NMDAR antagonist, led to a reduction in dendritic spines in the striatum of mice. The goal of our study was to determine the effect of acute and chronic ketamine and MK-801 treatment on spine density in the cortex and striatum, in order to reconcile the differences of these two studies. We determined that although acute ketamine (10 mg/kg) led to an increase in cortical spine density, a higher dose (20 mg/kg) did not. In addition, chronic ketamine treatment led to a reduction in spine density. On the other hand, MK-801 (0.2 mg/kg) had no significant effect on spine density in the cortex, but led to reduced striatal spine density. These results indicate that ketamine has dose-dependent, drug regimen and brain region specific effects on spine density. Furthermore, different NMDAR antagonists have differential effects on spine density. Therefore, further consideration needs to be made before introducing NMDAR antagonists as antidepressants as they can have detrimental effects on dendritic spine density.

2-C-65 Src-mediated activation of Pannexin-1 is a key perpetuator of ischemic cell-death

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Ischemic stokes induce stints of oxygen/glucose deprivation (OGD) to neural tissue downstream of an arterial occlusion, leading to subsequent dysfunction of neurons and ultimately cell death. It is widely accepted that ischemia-induced cell death is principally mediated by N-methyl-D-aspartate (NMDA) receptors via glutamate excitotoxicity; an observation in both acute hippocampal slices (CA1 pyramidal neurons) and in primary cultures (in vitro). This longstanding view of the importance of NMDA receptors in cell death has become expanded in recent years by the discovery of other ion channels, such as pannexin-1 (Panx1). Activation of Panx1 has been implicated both in ischemic and NMDA receptor mediated depolarizations, and more recently, we have shown Panx1 to be directly activated by an interaction with Src Family Kinases (SFKs) at the Panx1 c-terminus. To address the role of SFK-Panx1 activation in cell death, we measured calcium-influx in bulk loaded CA1 primary cultures in the presence of a novel SFK-Panx1 interfering peptide, TAT-Panx305-318. Bath application of TAT-Panx305-318 significantly reduced calcium influx in OGD. This was similar to our report using whole-cell recordings and indirect pharmacological block of Panx1 currents with the SFK antagonist PP2. Addition of the NMDA receptor pore blocker, MK801, significantly reduced both the calcium influx, as well as increased the survivability in OGD, but MK801 was not as effective as TAT-Panx305-318. We conclude that the newly identified NMDAR-SFK-Panx1 pathway is critical for perpetuating cell death during ischemia.

2-C-66 Sleep-wake disturbance and visual impairment precede reports of Parkinson's disease

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Parkinson's disease (PD) is characterized by motor symptoms, such as resting tremor, bradykinesia and postural instability. However, it is increasingly recognized that non-motor symptoms may be present for several years prior to a diagnosis. We examined whether specific non-motor symptoms at the preclinical stage predicted a future report of PD. Secondary analyses were conducted on 31,115 participants of the Survey of Health Aging and Retirement in Europe. At baseline, 14,469 participants reported the absence of PD and of significant motor impairment, and the absence of Alzheimer's disease or dementia at either follow-up time point. After an average of 2.3 and 6.6 years, 33 and 34 subjects reported PD, respectively. After controlling for age, sex, education, and body mass index, those that scored higher on a 7 factor sleep disturbance index, consisting of measures related to sleep and wakefulness, were at an increased risk of PD only at ~2 years. However, those who reported being smokers at baseline did not exhibit this effect of the SDI. After adding the 'use of glasses' to our model, visual impairment was also predictive of PD only at ~2 years. A report of 'stomach and intestinal problems' (e.g., constipation), was not a significant predictor at either time point. Finally, those with a history of smoking exhibited a decreased risk of PD at ~6 years. These findings suggest that symptoms related to sleep-wake disturbance predict future reports of PD with a relatively short latency, while reports of smoking appear to be protective against the disease.

2-C-67 The Parkinson's disease linked pesticide, ziram, shows differential effects at functionally distinct nerve terminals in a Drosophila model

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Parkinson's disease (PD) is a neurodegenerative disease characterized by the loss of dopaminergic neurons in the substantia nigra. The majority of PD cases are sporadic and the causes remain unclear, however, environmental exposures to toxins, such as pesticides, have long been suspected to play a role. Recent epidemiological data demonstrates that exposure to the pesticide ziram significantly increases the risk of PD, however, little is known regarding ziram's effects on neuron function and

health. We have utilized the Drosophila neuromuscular junction (NMJ) preparation to develop a novel model of ziram exposure in an intact synapse. We developed a genetic 'pHluorin' construct, consisting of a pH-sensitive form of GFP on the lumenal loop of the Drosophila vesicular monoamine transporter (DVMAT). Using this construct we conducted live imaging of synaptic vesicle fusion and reuptake (exo- and endocytosis, respectively) at the NMJ. We report that exposure to the PD-linked pesticide ziram significantly alters the essential neuronal processes of exocytosis and endocytosis. Interestingly, we find that functionally distinct nerve terminals (i.e. aminergic versus glutamatergic) are differentially susceptible to ziram exposure. Calcium imaging conducted using GCAMP, a calcium sensitive form of GFP, demonstrates that in addition to differences in exocytosis and endocytosis upon ziram exposure, calcium signaling is disrupted in distinctly different manners in glutamatergic versus aminergic nerve terminals.

2-C-68 scyllo-Inositol facilitates clearance of amyloid-beta peptide and huntingtin aggregates through distinct proteolytic mechanisms

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scyllo-Inositol, an endogenous inositol stereoisomer, has been tested in clinical trials for treatment of Alzheimer disease (AD) patients with respect to its activities in reducing toxic amyloid-beta peptide (Aß) aggregates. To further characterize its mechanism of action, we investigated whether binding of scyllo-inositol to aggregated proteins facilitates their clearance through proteolytic pathways. We compared the effects of scyllo-inositol on two clinically significant proteins, Aß and huntingtin (Htt). The effects of scyllo-inositol on Aß were examined in TgCRND8 mice that accumulate Aß aggregates and harbor AD-like pathology. The effects of scyllo-inositol on Htt were tested in the Htt14A2.5 PC12 line that over-produces polyglutamine-containing Htt aggregates. We found that un-treated TgCRND8 mice showed over-accumulation of Aß-containing autophagic vacuoles due to lysosomal deficits. Proteasome activity was also impaired compared to non-transgenic controls. scyllo-Inositol treatment rescued these changes together with a reduction of Aß accumulation in autophagosomes and lysosomes. In contrast, in Htt14A2.5 cells, autophagic activity in Htt-over-expressing cells was not altered while lysosomal and proteasomal activities were decreased compared to cells not over-producing Htt. scyllo-Inositol treatment reduced the level of aggregated Htt and this effect was found to be mediated by the lysosome and the proteasome but not by autophagy. In conclusion, scyllo-inositol promotes clearance of Aß and Htt aggregates through distinct proteolytic pathways.

2-C-69 Effects of Embryonic Ethanol Exposure on the Anatomy of Adult Zebrafish Brain

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Exposure to alcohol during development can result in a range of abnormalities in the central nervous system from severe to mild depending on the dose. The level of neurogenesis in the adult brain has been linked to the brain function of the normal and diseased brain. Here we analyze the effect of low embryonic alcohol exposure on the anatomy of the zebrafish brain. The level of alcohol exposure we employ is more realistic from the perspective of fetal alcohol spectrum disorders (FASD). We expose the zebrafish to alcohol at 24 hours post-fertilization (hpf) for 2 hours using three concentrations, 0.00%, 0.50% and 1.00% (EtOH vol/vol%). Briefly, adult zebrafish were sacrificed by decapitation and the heads were rapidly fixed in 4% paraformaldehyde. 30µm sagittal sections were cut using a cryostat and processed for Nissl body staining. Briefly, brain sections were hydrated with distilled water, immersed into 1% cresyl violet for 3 min, dehydrated in an alcohol series, cleared in xylene and cover slipped. The number of cells in the different brain regions are being analyzed using

Image ProPlus and differences between treatment groups are currently being completed. It is likely that developmental ethanol exposure results in a change in the level of neurogenesis in the brain. Reduction in neurons or cell population in the central nervous system may be responsible for neurobehavioural effects associated with FAS in humans. Given the translational relevance of zebrafish, this will facilitate the cellular mechanisms underlying the effects of embryonic alcohol exposure in humans.

2-C-70 The role of medial prefrontal cortex synapsin II on executive function in a pre-clinical animal model and implications for schizophrenia therapy

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Schizophrenia is a debilitating mental disease with a global prevalence of 1%. Despite its long history, its pathophysiology remains elusive. The urgent need for this knowledge is unremitting, as its discovery yields the long-sought therapeutic cure. As of yet, current treatment focuses on the symptoms: positive (e.g. hallucinations and delusions), negative (e.g. social withdrawal), and cognitive (e.g. executive function deficits). An emerging association is being realized between the pathophysiology of schizophrenia and the expression of neuron-specific phosphoprotein synapsin II, which facilitates neurotransmitter release. Our laboratory has previously shown that synapsin II expression increases following haloperidol treatment, is decreased in the prefrontal cortex in post-mortem schizophrenic patients, and knockdown of synapsin II in rats emulates the sensorimotor gating, locomotor, and social interaction deficits characteristic of schizophrenic patients. The present study contributes to the portfolio of synapsin II by using antisense deoxyoligonucleotide knockdown technology to reduce synapsin II expression and investigate its effects on one cognitive domain--executive function--using the rodent attentional set-shifting task. Altogether, this study highlights the role of synapsin II on a schizophrenic cognitive symptom--with clear implications for therapy--and progresses the field towards uncovering the pathophysiology of schizophrenia. This work was funded by the Canadian Institutes of Health Research (CIHR).

2-C-71 Lacosamide reduces spontaneous excitatory and inhibitory postsynaptic potentials and is anticonvulsant in an in vitro neocortical seizure model

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Previous behavioural and electrophysiological studies have indicated that lacosamide (LCM) acts as an anticonvulsant drug in vivo. The purpose of the present study was to investigate the effects of lacosamide in an in vitro model of epilepsy. Dual extracellular field potential and intracellular whole cell recordings were obtained from 30-60 day old mouse cortical slice preparations. Recordings from layer II/III of the frontal cortex during application of 4-aminopyridine (4-AP) (100µM) showed spontaneous and recurrent epileptiform activity. Application of LCM (100µM) strongly inhibited spontaneous epileptiform activity induced by 4-AP and ensuing seizure activity. LCM produced a significant reduction in the incidence of spontaneous excitatory postsynaptic currents (EPSC's) and inhibitory postsynaptic currents (IPSC's) in cortical cells exposed to 4-AP. The results indicate the potential for LCM to inhibit epileptiform activity in an in vitro animal model of epilepsy, and support its role in seizure reduction observed in clinical trials.

2-C-72 Longitudinal diffusion tensor imaging and neuropsychological correlates in breast cancer patients undergoing chemotherapy

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Converging evidence from functional magnetic resonance imaging and neuropsychological studies now provides solid empirical support for the existence of chemotherapy-related cognitive impairment (CRCI); however, the underlying brain mechanisms of these symptoms are still poorly understood. Damage to white matter (WM) is thought to play a role in CRCI. The current study used diffusion tensor imaging to identify WM changes in a group of 19 breast cancer patients and 19 individually matched healthy controls at three time points (t1, baseline; t2, post-chemotherapy; t3, 1 year post-chemotherapy). Participants also completed a neuropsychological test battery at each time point. Tract-based spatial statistics were used to perform whole-brain voxelwise analyses of fractional anisotropy (FA, a measure of fibre tract integrity), with mood and anxiety included as covariates. Results revealed no significant changes in FA in controls (t1-t2, t1-t3). There was a significant reduction in FA ($p<0.01$) in the patient group post-chemotherapy in the dominant left hemisphere involving the frontal white matter, anterior body of corpus callosum, Broca's area, contralateral right medial thalamus, brachium pontis and cerebellar white matter. Reduced FA was also observed between t1 and t3, but changes were less prominent and disappeared when results were controlled for changes in mood and anxiety. These results suggest that chemotherapy alters white matter structural integrity but that this might reverse with time, and that affective factors may explain part of the observed effect.

2-C-73 Acute stress and inflammation alter neuromodulator effects on cortical networks

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Neurodegenerative diseases are commonly associated with alterations in neuromodulatory networks. As animal studies have shown that inflammation is a key component in neurodegenerative processes and that acute stress can actually exacerbate infection induced neuroinflammation, we hypothesized that properties of the neuromodulator-mediated regulation of neural networks would be altered in animals subjected to acute stress followed by a systemic inflammatory insult. Neuromodulator effects on GABA-dependent paired-pulse suppression were assessed in mouse cortical slices with or without pre-treatment. Under control conditions the neuromodulators reduced first pulse amplitude with less effect on the second, resulting in an increase in the paired-pulse ratio (Fig. 1C inset). The effects on the ratio were reduced in treated (Fig. 1C) mice despite no change in neuromodulator effects on the baseline eEPSP amplitude (Fig. 1D). The degree of baseline inhibition in the treated animals was also significantly lower than control (Fig. 1B), supporting the notion that neuromodulators act through control of inhibitory processes. These studies demonstrate that inflammatory-mediated changes in cortical GABA inhibition can affect neuromodulator-mediated regulation of cortical connectivity and thus behavioral state. Improved understanding of factors that impact neuromodulator-mediated shaping of network connectivity will enhance understanding of the functional overlap between psychiatric and neurodegenerative processes.

2-C-74 Rest and action tremor profiles across a wide range of loads in PD and ET patients over sequential neurotoxin injections

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While PD tremor is thought to be predominantly at rest (no load=minimal muscle activation) and ET tremor with action (with load=range of muscle activation to maximum), tremor may be present across the whole range of load conditions. BoNT A is a possible treatment for upper limb tremor in

both disorders. However, the effect of BoNT A on ET and PD tremor over a range of loads has not been studied. Similarly the weakness produced as a side effect may also differ over serial injections. Both the profile of the tremor and the weakness produced by BoNT A after such serial injections needs to be understood to optimize treatment. The objective is to evaluate in a series of sequential neurotoxin injections the pattern of change in: (1) rest versus action tremor across a wide range of loads in PD and ET and BoNT A effect at each load condition; (2) weakness profile in individual fingers and the grip strength. 7 clinically diagnosed ET (age 72±7) and 10 meeting the UK Brain Bank Criteria for PD (67±7) but not responding to oral medication were enrolled in the study. Kinematic assessment tools were used at baseline and two follow up visits (6 and 10 weeks after injection) to measure possible degrees of freedom at all joints along with finger pressure. All trials were repeated three times at each visit. The data were analysed to show tremor amplitudes at all joints and loads. Further, average of finger strength was evaluated. The profiles of the changes over serial injections in tremor amplitude across load parameters and weakness over the visits will be shown.

2-C-75 Increased doublecortin expression in the olfactory bulb of unmedicated depressed suicides

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Adult brain neurogenesis (ABN), the process by which adult-born neurons are incorporated into existing neural circuitry within the hippocampal dentate gyrus (DG) and olfactory bulb (OB), has been implicated in the etiology of major depressive disorder (MDD). To date, most investigations have focused on ABN within the DG, which has been shown to mediate some of the effects of pharmacological antidepressant treatment (ADT). Few studies have explored the role of OB neurogenesis in the etiology and treatment of MDD. In the present study, we employed immunoblotting to measure the expression of well-established protein markers of neurogenesis in post-mortem OB samples from depressed suicide completers (DS; n = 16) and psychiatrically-healthy controls (CTRL; n = 10). No significant differences were found in expression of proliferating cell nuclear antigen (PCNA; a marker of proliferating cells) or calretinin (CR; a marker of immature OB interneurons) between DS subjects and CTRLs. However, DS subjects displayed elevated doublecortin (DCX; a marker of migrating neuroblasts) protein levels as compared to CTRLs ($p = 0.044$). When DS subjects were subdivided into those receiving/not receiving ADT at time of death, only unmedicated DS subjects displayed higher DCX than CTRLs ($p = 0.016$). These results suggest that OB neurogenesis may be altered in unmedicated DS subjects, and that ADT reverses this increase. We are currently investigating whether this elevated DCX expression is associated with specific alterations of cellular morphology granule cell density and DCX-IR cell morphology).

2-C-76 Chemical and environmental factors during early development alter measures of attentional processing in adult rats

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Attentional processing is a higher order cognitive behaviour found to be disrupted in a variety of human neuropsychiatric disorders. Many brain areas involved in attentional processing can be influenced during development, resulting in long lasting changes to the adult central nervous system (CNS). Research in our lab has shown that rats treated neonatally with the glutamate agonist domoic acid (DOM) during a critical period of CNS development display a variety of subtle cognitive changes in adulthood that suggest alterations to attentional processing. The goal of this research was to investigate the role of chemically (DOM) and environmentally (isolation rearing) induced changes in brain development on behavioural and

neurochemical measures of attentional processing. Sprague Dawley rats (n=96) were treated daily with 20 µg/kg of DOM or saline (controls) from postnatal days (PND) 8-14, a time of rapid brain growth and change. On PND 21 rats were housed either alone or in groups of four. As adults, rats were tested for both latent inhibition (LI) and prepulse inhibition (PPI); measures of attentional and sensorimotor processing. Results indicate that male DOM-treated rats displayed significantly lowered LI regardless of housing condition. Additionally, DOM treatment and housing condition were found to have a significant effect on both the average PPI and the latency to startle of both male and female rats. Following testing, rats were euthanised and fresh brain tissue was dissected, flash frozen and stored for later analysis of relevant protein expression.

2-C-77 Magnetic Resonance Spectroscopy and Diffusion Tensor Imaging in Cervical Myelopathy Patients Following Spinal Decompression Surgery

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The goal was to characterize cortical metabolite levels using 1H magnetic resonance spectroscopy (MRS) and white matter (WM) integrity with Diffusion Tensor Imaging (DTI) in cervical spondylotic myelopathy (CSM) following spinal decompressive surgery. Twenty-seven CSM patients underwent 2 MRI scans on a 3.0T Siemens Magnetom Tim Trio before and 6 months following surgery. Ten healthy controls had 2 MRI scans 6 months apart. Areas of activation from fMRI scans of a finger-tapping paradigm were used to localize a spectroscopy voxel on the greater deficit side of the motor cortex in CSM group and on each side of the motor cortex in controls. Regions of interest (ROI) for DTI analysis were defined for each subject in the WM adjacent to the motor and sensory cortices of the hands and entire cerebral WM. Pre-operatively, CSM group showed lower NAA/Cr (1.20±0.06) and higher Cho/Cr ratio (0.52±0.02) compared to controls (1.38±0.04; 0.58±0.02, $p<0.05$,respectively). Post-surgery, NAA/Cr ratio was lower in CSM group (1.10±0.06) compared to controls on the left (1.39±0.05; $p<0.0001$) and right side (1.36±0.08; $p=0.02$). DTI measures were not different in any ROI at any time point. The change in NAA/Cr ratio in CSM group correlated with the change in mJOA clinical score ($r=-0.43$; $p=0.01$). Following successful surgery and functional gain, the WM tracts remained intact while the NAA/Cr concentrations remained depressed, suggesting limited capacity for recovery of the metabolic profile of the motor cortex and that recruitment of surrounding cortex may be necessary for functional recovery.

2-C-78 Influence of the Huntingtin Protein in the Regulation of Ciliogenesis and Abnormal Ciliary Function Observed in Huntington's Disease

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The primary cilium is a sensory organelle on the majority of mammalian cell types. Dysfunction of normal cilia structure or function leads to a broad spectrum of diseases known as ciliopathies. Huntington's disease (HD) is a devastating neurodegenerative disorder caused by an abnormal polyglutamine expansion in the huntingtin protein. Proteins of the huntingtin interactome exhibit associations with ciliary structures or proteins but little investigation into the role of huntingtin in the primary cilium has been performed. Through immunofluorescence, we have demonstrated that huntingtin localizes within the compartment of the primary cilia, unless phosphorylated at two critical serine residues within the amino-terminus, which causes huntingtin relocalization to the basal body. This suggests that a phosphorylation dependent switch regulates the localization of huntingtin to different components of the primary cilium. Using advanced live-cell imaging techniques, we observed primary cilium dynamics were varied between mutant and wild type cell types. Alterations in primary cilium dynamics could alter a number of downstream signalling pathways, which initiate in the cilium. Finally, using a powerful inhibitor of CRM-1 dependent export, leptomycin B, we noted

an increase in the presence of huntingtin in the primary cilium. While the significance of these findings to disease have yet to be elucidated, we hypothesize that wild type huntingtin is essential in proper primary cilium function.

2-C-79 Rhythmic Features of Seizure-Like Events in Human Temporal Neocortical Slices

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Purpose: We investigated the rhythmic properties of seizure dynamics of human temporal neocortical tissue. Methods: Middle temporal neocortical tissue was resected from 5 surgical candidates with mesial temporal lobe epilepsy. 500 µm coronal cortical slices were placed in artificial cerebral spinal fluid and extracellular electrophysiological recordings were obtained from superficial (layers 2/3) and deep (layer 5) neocortical layers. Kainate (50 nM) and carbachol (50 µM) were used to mimic inhibitory and excitatory drives, respectively (Buhl 1998 et al. J. Physiol 1998;513:117-126). Of those slices that showed activation, 10% showed spontaneous seizure-like events lasting 35 +/- 25 seconds. Phase coherence (Lachaux JP et al. Hum Brain Mapp 1999;8:194-208.) and modulation index (Tort A et al., J Neurophysiol 2010;104:1195-1210) were used in the frequency analysis. Results: Two trends were consistently noted upon transition into seizure: 1.) The lower frequency involved in CFC transitions from a delta (0.5-4 Hz) rhythm, to a theta (4-8 Hz), alpha (8-15 Hz) or beta frequency. All of these lower frequencies were coupled to rhythms in the gamma (>30 Hz) and high gamma (>150Hz) range. 2.) There was a consistent loss of phase synchrony between cortical layers in the delta range at seizure onset. Transition out of seizure was consistently associated with a return of the lower delta CFC rhythm. Conclusion: We describe a feature set involving PC between and CFC within superficial and deep layers of the human temporal neocortex as related to seizure dynamics.

2-C-80 Evaluating the Warburg effect and amyloid-beta resistance in a transgenic Alzheimer's disease mouse model

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Numerous studies of post-mortem brain tissue found significant amyloid plaque deposition in elderly individuals with no symptoms of Alzheimer's disease (AD). It is believed that asymptomatic individuals with high plaque load likely had undiagnosed mild cognitive impairment. However, we propose that some of these individuals may have developed resistance to the toxic effects of amyloid-beta (Aβ) peptide, a principle component of plaques. We previously demonstrated that Aβ resistant nerve cells exhibit elevated expression of pyruvate dehydrogenase kinase 1 (PDK1), a central mediator of the Warburg effect; a form of metabolism frequently employed by cancer cells as an anti-apoptotic strategy. Immunoblot analysis of cortical extracts from juvenile transgenic (tg) AD (APPswe/PSEN1dE9) mice revealed elevated PDK1 expression whereas PDK1 expression was decreased in cortical extracts from 12 month old tg-AD mice compared to controls. The differential expression of PDK1 in young versus old tg-AD mice correlates with age-dependent cognitive decline. To determine if elevated PDK1 expression in young tg-AD mice contributes to Aβ resistance, we treated mice with dichloroacetate (DCA), a chemical inhibitor of PDK1. In vivo 1H magnetic resonance spectroscopy revealed that lactate levels, a product of the Warburg effect, were elevated in young tg-AD mice but decreased following DCA treatment. These findings suggest that elevated PDK1 expression promotes a shift to a protective from of brain metabolism in young tg-AD mice; a finding that may have relevance to the treatment of AD.

2-C-81 Neural Precursor Proliferation and Migration following an ET-1 Induced Focal Ischemic Injury in the Adult Mouse Cortex

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The endogenous neural precursor population responds to an ischemic insult by proliferating to produce neuroblasts which have the capacity to migrate and differentiate into neurons, astrocytes and oligodendrocytes. Neuroblasts therefore, have the potential to repair the brain. It is controversial as to whether endogenous neuroblasts can truly differentiate into functional neurons which integrate into the neural network or whether they function as a source of trophic support. A challenge to addressing this question is while numerous neuroblasts are produced and migrate to the site of an infarct, the majority die before differentiating into functional neurons. To determine whether neuroblasts can affect neural regeneration, we propose to enhance neuroblast survival by manipulating the expression of pro-survival gene, Mcl-1 selectively in neuroblasts. Our lab has recently developed a reproducible focal ischemic injury model in the mouse forelimb motor cortex. To determine the optimum time window in which to transfect neural precursors, we have identified the peak proliferative and migratory response of neural precursors to an ischemic insult.
Acknowledgements: This work was supported by an operating grant from the Canadian Institutes of Health Research and the Research and Development Fund of Newfoundland and Labrador to JV. RFB is supported by a Heart & Stroke Foundation Centre for Stroke Recovery Studentship, and RBR was funded by a Keith Griffiths Heart & Stroke Foundation Student Award.

2-C-82 "Filling The Gap": Connexins In The Mouse Model Of Fetal Alcohol Syndrome

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Maternal alcohol exposure during gestation can cause serious injury to the fetus, resulting in the fetal alcohol syndrome (FAS), which is associated with a range of physiological and behavioral impairments, including seizure susceptibility. Objectives: We developed a mouse model of the FAS to study: i) the in vitro electrophysiology and epileptiform activity in mouse hippocampal slices, and ii) the underlying molecular and biochemical changes associated with the altered neurophysiology. Methods: C57Bl6 pregnant mice were exposed to 10 % v/v ethanol for the first trimester of gestation by voluntary consumption. Using acute brain slices prepared from control and ethanol-exposed pups of age PD 15 to PD 21, extracellular field potentials were recorded from the CA3 and CA1 hippocampal regions.Several candidate molecules involved in electrical neurotransmission were analyzed for changes in their mRNA and protein expression following the prenatal ethanol exposure by q-PCR and immunoblotting assays respectively. Results: Prenatal alcohol exposure for the first trimester resulted in an increase of spontaneous field activity of depolarizing potentials between 0.2 to 1mV in amplitude and 30-150 ms in duration, in both the CA3 and CA1 hippocampal regions. Furthermore, prenatal alcohol exposure resulted in an increase in spontaneous and recurrent seizures in the CA3 and CA1 hippocampal regions which were blocked by the application of the gap junctional communication antagonist, carbenoxolone.In addition, we observed up-regulation of Cx30 mRNA and Cx30 protein in the hippocampus of FAS.

2-C-83 Role of p53 in Radiation-Induced Inhibition of Hippocampal Neurogenesis

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BACKGROUND: Cranial irradiation ablates adult neurogenesis in the dentate gyrus. p53 activation following radiation triggers post-radiation events that help to maintain genomic integrity by activating cell-cycle arrest, DNA repair and/or cell

death. OBJECTIVE: To investigate the role of p53 in neurogenesis after radiation in the dentate gyrus. METHODS: Adult male C57 mice with 0 (p53KO), 1 (p53+/-), 2 (p53+/+), or 3 (SP53) copies of p53 gene were given cranial radiation and neurogenesis in the dentate gyrus was assessed at 9 weeks following a BrdU incorporation assay. RESULTS: p53 deficiency was associated with increased neurogenesis in the dentate gyrus, whereas profound inhibition of neurogenesis was observed in p53 deficient mice after a single dose of 5Gy. Similar results were observed after a fractionated radiation schedule. The number of dual NeuN/BrdU-positive cells was lower in SP53 mice compared to p53+/+ mice, but the extent of neurogenesis inhibition after 5 Gy was not different between the two groups. No difference in the number of newborn type I cells and activated microglia was observed in control and irradiated p53KO compared to p53+/+ mice. CONCLUSION: The number of p53 gene copy correlates negatively with adult neurogenesis in the dentate gyrus. Deficiency in p53 is associated with profound inhibition of neurogenesis after irradiation, and this does not appear to be related to changes in microglia activation or early neural progenitor populations. An additional p53 gene does not confer protection against radiation induced inhibition of neurogenesis.

2-C-84 Targeting ET-1 to the anterior portion of the forelimb motor cortex reliably produces ischemic infarcts with behavioural deficits

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Recently there is excitement in manipulating neural precursor cells (NPCs), as they migrate toward cortical infarcts and differentiate into neurons and glia. To assess functional recovery by neural regeneration after an ischemic injury, a focal injury model is required. Here, Endothelin-1 (ET-1, a vasoconstrictive peptide) was assessed for its ability to reliably produce an ischemic injury causing behavioural deficits and NPC migration. Mice were trained and tested on the mouse staircase and forelimb asymmetry tasks. A focal ischemic lesion was produced by intracortical injection of ET-1 into the forelimb motor cortex (FMC). Histology was performed to analyze the volume, shape and depth of the infarct. The mouse staircase test was found to specifically predict damage to the anterior FMC, highlighting the functional subdivisions of the FMC. A sensitive novel analysis of the forelimb asymmetry test, "paw-dragging", also predicted ischemic injury to the FMC. Probability maps were constructed, such that the cortical area responsible for specific behavioural deficits can be accurately targeted. Furthermore, NPC migration toward the injured cortex was observed for the first time after mouse intracortical ET-1 injection. This reproducible ischemic injury model lends itself to manipulating NPCs for regenerative therapies. Acknowledgements: This work was supported by an operating grant from CIHR and RDC-NL to JV. RFB is supported by a Heart & Stroke Foundation Centre for Stroke Recovery Studentship, and RBR was funded by a Keith Griffith's Heart & Stroke Foundation Student Award.

2-C-85 Hippocampal expression of neuregulin-ErbB and neurogenesis-related markers in suicide completers

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INTRODUCTION: Neuregulin-1 (NRG1)-ErbB signaling has been suggested to modulate affect and hippocampal plasticity, and to underlie the etiology of psychiatric disorders. We have shown that peripheral NRG1 administration has antidepressant-like effects and increases adult ventral hippocampal neurogenesis, potentially through binding to ErbB3 receptors on SOX2-expressing dentate gyrus (DG) cells. We have also reported that ErbB3 expression is reduced in the hippocampus of suicide completers relative to controls. Our current work examines expression of

neurogenic markers and ErbB receptors in the hippocampus of suicides and controls. METHODS: Samples were obtained from the Douglas-Bell Canada Brain Bank and processed for quantitative real-time PCR and immunohistochemistry. Subject groups were matched for age, tissue pH, and post-mortem interval. RESULTS: ErbB3-immunoreactivity was present in the human DG. Hippocampal expression of SOX2 was not significantly reduced in suicide completers, although SOX2 expression correlated significantly with ErbB3 expression. NRG1 expression in the hippocampus was unaltered. Preliminary assessment of numbers of calretinin putative immature neurons did not reveal group differences. CONCLUSIONS: These preliminary results suggest that decreased hippocampal ErbB3 expression in suicide completers may occur in the absence of NRG1 expression changes, and support the association between ErbB3 and SOX2 expression in the hippocampus. We are currently assessing methylation of ErbB3 as well as additional neurogenic markers. Support: CIHR and FRQS.

2-C-86 From snakebites to Alzheimer's disease: Exploring traditional Maya medicines for novel phospholipase A2 inhibitors

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Converging evidence suggests a pivotal role for phospholipase A2 (PLA2) enzymes in Alzheimer's disease (AD) pathology. The PLA2s were first characterized from snake venom and are responsible for the cleavage of fatty acids from the sn-2 position of membrane glycerophospholipids. Several forms of PLA2, including the secreted PLA2s (sPLA2s), have been detected in the human brain. Each play a fundamental role in membrane remodeling and the generation of second messengers. In AD, the group V sPLA2 isoform is upregulated and is thought to mediate membrane remodeling during calcium overload in affected neurons. Pharmacological inhibition of group V sPLA2 may reduce the aberrant membrane remodeling associated with neuronal injury. Here, we used an ethnobotanical approach to identify group V sPLA2 inhibitors. Since a major component of snake venom is sPLA2, we hypothesize that botanical medicines used by traditional healers to treat snakebites contain phytochemical sPLA2 inhibitors. Q'eqchi' Maya healers in Belize were interviewed and botanical snakebite remedies identified. Cited plants were collected, taxonomy determined, and extracts prepared in 80% ethanol. Ethanolic extracts were screened using an in vitro enzyme assay for direct inhibition of human recombinant group V sPLA2. Overall, four plant species were cited by healers and tested for inhibitory activity. Plant 'MWT27' was found to inhibit sPLA2 activity by 33.3%. This suggests the presence of sPLA2 inhibitory phytochemicals, which can be identified by bioassay-guided fractionation and tested for neuroprotective activity.

2-C-87 Induced pluripotent stem cell-derived neurons from autistic individuals with microdeletions of the PTCHD1 locus

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The study of neuropsychiatric disorders and the development of effective treatments have been limited by a lack of appropriate models. Induced pluripotent stem (iPS) cells represent a potentially limitless supply of personalized neurons for disease modeling. A high priority autism risk allele is the PTCHD1 locus, which encodes both the PTCHD1 gene - a brain-specific regulator of the hedgehog-signalling pathway - and divergently transcribed long non-coding (nc) RNAs of unknown function. We have generated iPS cells from an autistic proband encoding a genomic deletion that disrupts both PTCHD1 and the ncRNAs, a second autistic proband with a deletion that exclusively disrupts the ncRNAs, and the unaffected mother of the first proband. iPS lines are pluripotent, retain autism-associated microdeletions, and exhibit no evidence of additional clinically significant genomic copy

number variations. Control iPS-derived neurons express both the PTCHD1 gene and ncRNAs. As expected, the microdeletion that encompasses the PTCHD1 gene and ncRNAs disrupts expression of both genes. iPS-derived neurons with a microdeletion upstream of PTCHD1 do not express the ncRNAs, but express normal levels of PTCHD1. PTCHD1-null neurons respond normally to an agonist of the hedgehog pathway and exhibit normal soma size. We are currently analyzing dendritic morphology, synapse formation, and gene expression in iPS-derived neurons. These experiments will contribute to our understanding of the cellular and molecular etiology of autism, and may provide valuable insights into how autism may be treated.

2-C-88 MicroRNAs deregulated early in prion disease may contribute to a neuroprotective mechanism

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Prion diseases are caused by the conversion of the normal prion protein (PrPC) into the infectious form (PrPSc) and with time, the accumulation of PrPSc leads to neuronal dysfunction and death. Nevertheless, how PrPSc causes neuronal dysfunctions remains unknown. Investigating molecular changes that occur early in disease, when PrPSc is beginning to accumulate, may hold promise in identifying these neurodegenerative pathways. We performed high-throughput transcriptomic and miRNomic temporal screens on a neuronal-rich region (CA1 hippocampus) to obtain profiles of transcripts and their regulatory small RNAs, respectively. We identified the presence of a neuroprotective response that occurs in these neurons during pre-clinical disease and as disease progressed, this protective response diminished. We validated 7 miRNAs to be upregulated during early prion disease of which 3 had known neuroprotective function. Since miRNAs are global gene regulators, better understanding of their involvement, and therefore, function within the context of neuroprotection may reveal possible avenues for therapy development. We are currently characterizing neuronal-specific function for the 4 miRNAs using target prediction programs and experimental approaches. These 4 miRNAs can potentially regulate numerous neuron-specific genes, many of which have morphological functions. Luciferase assays are currently underway to validate these predictions. Also, miRNA concentration in post-mitotic mouse primary neuronal cultures will be manipulated to assess possible effects on neuronal morphology.

2-C-89 Huntingtin is a Non-Lumenal ER Stress Sensor That Can Halt Cytoskeletal Dynamics

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The Huntington's disease (HD) protein, huntingtin, is an essential 350KDa protein present in all cell types. We have characterized a 17 aa, domain in huntingtin, N17, that associates with the ER. By the use of live cell imaging under stress, we can show that huntingtin has both a fast and a slow stress response that causes the protein to relocate from the ER to the nucleus and the early endocytic machinery, as well as nuclear actin. This translocation event is mediated by phospho-signaling on two critical serines in N17. Mutant huntingtin in HD is hypo-phosphorylated in N17, and is thus defective in this stress response. We hypothesize that this large scaffolding protein has a critical role in stress response in highly dendritic neuronal cells in halting cytoskeletal rearrangement to transiently free ATP. Using live cell Fluorescence Lifetime imaging (FLIM) and Förster resonant energy transfer (FRET), we can show a critical conformational switch of huntingtin that is impaired by the polyglutamine expansion in HD. This conformational change can be detected in endogenous huntingtin in HD patient fibroblasts, and at the critical disease threshold of CAG repeats in HD. We will present data from a chemical biology study that outlines the role of the CK2 pathway in

this stress response, as well as animal model data that shows a striking reversal of the HD phenotype by compounds that restore the proper signaling, and conformation of the mutant huntingtin protein.

2-C-90 Automatic Multisensor Detection of Freezing of Gait in Parkinson Disease

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Background: FOG is a highly debilitating symptom associated with progression of PD severity. Automatic, objective and comprehensive ambulatory assessments of FOG would be beneficial for study of the phenomenon as well as clinical judgement. A wireless foot-sensor based system with untethered kinematic measurement systems allow for the application of automatic algorithms to detect FoG episodes. Long term monitoring of freezing duration and frequency will help with characterizing FOG and treatment strategies. Methods: 20 PD patients with clinical history of PD and FOG will be completing the study. Data will be collected from in-shoe pressure sensors, two 3-D accelerometers, one electro-goniometer on right knee, one electro-inclinometer on right hip, and one electro-inclinometer on the chest in 6 in laboratory, and 6 free gait tasks most representative of daily in-home walking. Data is run through an algorithm for FOG episode detection. Results: The on-going kinematic and foot-pressure data analyses shows that freezing episodes are reliably captured and identified. Distinct patterns captured by each detection modality allows for accurate detection of FoG by the algorithm. Results of the algorithm will be validated via correlation between in-lab video footage and in-home data. The trained algorithm by in lab data could be used to identify in-home episodes of FoG. Personalized evaluation of freezing frequency and duration may suggest a personalized management strategy for each Parkinson's patient through in-home severity monitoring.

2-C-91 Variations within microRNA-binding sites in genes involved in neurodegeneration

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Genetic variability in the form of SNPs in miRNA target sites should represent a starting point for the discovery of novel germline markers of susceptibility to conditions that may contribute to neurodegeneration in humans. With this goal in sight, we employed an in silico approach to screen for the presence of SNPs in the 3'UTR of 125 genes implicated in prion-induced neurodegeneration. The potency of SNPs in altering miRNA::mRNA interaction was evaluated by performing in silico hybridization of a miRNA with the 3'UTR of an mRNA in the presence of the common or variant allele. Difference in the free energies of binding between the two alleles was computed as variation of ΔG (i.e. ΔΔG) and an indication of whether the occurrence of an SNP could impact on the interaction of the miRNA with the mRNA. We documented 113 SNPs in 53 of these genes. Characterization of the potency of the SNPs in altering miRNA::mRNA interaction through evaluation of the thermodynamics of RNA::RNA binding revealed that 42 SNPs increased the binding potential of miRNAs, while 57 decreased the binding potential, and 14 were neutral. Interestingly, we identified an abundance of SNPs among neuronal receptor genes, including genes coding for GABA-receptor subunits. We successfully validated, amongst others, the occurrence of rs9291296 in the 3'UTR of GABRα4 and its impact on the binding efficiency of miR-26a-5p. In general, our study could represent a starting point for the exploration of novel disease-associated germ line markers of susceptibility to human neurodegenerative conditions.

2-C-92 Parvalbumin Neuron Inhibition in the Ventral Hippocampus and Schizophrenia-like Behaviors in Mice

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GABA or parvalbumin neuron loss has been observed in several regions of postmortem schizophrenia brains, including the hippocampus. Animal models exhibiting reduced GABA or parvalbumin neurons show schizophrenia-like behaviours. Hyperactivity in the ventral hippocampus is proposed to underlie the positive symptoms of schizophrenia due to ventral hippocampal activation of the mesolimbic dopamine system. Ventral hippocampal hyperactivity may result from reduced GABA or parvalbumin neuron activity. To test this hypothesis, we selectively and reversibly inhibited GABA or parvalbumin neurons in the ventral hippocampus of mice using hM4D, an inhibitory designer receptor exclusively activated by designer drugs (DREADD). hM4D expression in GABA or parvalbumin neurons of the ventral hippocampus was achieved by infusing a Cre-dependent viral vector (AAV-FLEX-hM4D) into the ventral hippocampus of Gad65:cre or parvalbumin:cre mice respectively. In vitro bath application of clozapine-N-oxide (CNO) reduced the firing rate of parvalbumin neurons expressing hM4D in the ventral CA1. GABA neuron inhibition with CNO increased open field locomotor activity more than parvalbumin neuron inhibition. The effect of hM4D-mediated silencing of GABA or parvalbumin neurons on prepulse inhibition and amphetamine-induced locomotion was also examined. These data support the hypothesis that ventral hippocampal GABA neurons contribute to the positive symptoms of schizophrenia.

2-C-93 Inducing ischemic stroke in awake mice reveals that anesthesia can alter the efficacy of a stroke therapy

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Almost all promising experimental treatments of stroke have failed in human trials. One problem with experimental models of stroke is the use of general anesthetics which modulate excitatory and inhibitory neurotransmission, cell survival/death signalling pathways and blood flow. To avoid this potential confound, we developed a protocol for inducing focal ischemic stroke in the cerebral cortex of awake, unrestrained mice. Our results show that ischemic damage is significantly greater in awake mice versus those anesthetized with isoflurane during stroke induction. Next, we tested the efficacy of two putative neuroprotective drugs (NR2B and α4 nicotinic receptor antagonists) in preventing ischemic damage in awake and anesthetized mice. Unexpectedly, we discovered that that a pharmacological treatment could have no apparent impact on ischemic damage when the stroke was induced under anesthesia, but show significant neuroprotection when conducted in awake mice. These results suggest that many effective stroke treatments could have been missed in preclinical studies because of the use of general anesthetics such as isoflurane to induce stroke.

2-C-94 Analysis of high content fluorescence images by open-source software programs employing machine learning can identify compounds affecting huntingtin localization

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Huntington's disease is an autosomal dominant, neurodegenerative disorder caused by a polyglutamine expansion in the huntingtin protein. This expansion causes huntingtin to assume abnormal - and toxic - localizations and conformations. Recent research indicates that it is not just the localization and conformation of huntingtin that is important to its normal function, but also the stoichiometry of the protein. Over-expression of huntingtin fragments and a lack of high quality imaging data have hampered previous research efforts. The goal of our current project is to create a database of high content images of endogenous huntingtin using a set of monoclonal

antibodies for immunofluorescence spanning the entire length of huntingtin. This technique was used to screen a small library of natural compounds. Open-source software programs using supervised or unsupervised machine learning were employed to identify compounds that changed the localization, conformation or levels of huntingtin. Preliminary analysis using an antibody recognizing the first 17 amino acids of huntingtin identified several potential compounds that may trigger a change in the cellular localization of huntingtin. Validation of compounds by means of further imaging, FRET studies and biochemical methods will be necessary. In the future, additional high content databases with simultaneous imaging of multiple epitopes will be developed using small compound libraries. These databases can be used for data mining in the hope of identifying compounds that can modulate the toxicity of mutant huntingtin.

2-C-95 Lipids as regulators of adult neural precursor behaviour

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Aging results in a dramatic decline of neurogenesis within the two main neurogenic niches, the subventricular zone (SVZ) surrounding the lateral ventricles and the dentate gyrus of the hippocampus. Within these niches, combinatorial signals control stem cell self-renewal, proliferation, fate determination and differentiation. Previous studies have shown widespread changes in lipid metabolism during aging, including increased free fatty acids within tissue and plasma and abnormal lipid inclusions. In this study, we hypothesize that changes in lipid regulation are likewise present in the brain and involved in age-associated decreases in neural stem cell (NSC) activity, neurogenesis and cell replacement in the SVZ. Consistent with this hypothesis, we found that declining neurogenesis during aging is accompanied by an accumulation of lipid droplets within the SVZ. To better understand how this increasing local concentration of lipids within the SVZ could interfere with the neurogenic process, we isolated adult SVZ neural precursors using the neurosphere assay and treated them with increasing concentrations of lipid droplet-associated lipids (fatty acids and cholesterol). We found that neurosphere formation was inhibited when neural precursors where treated on day 1. Interestingly, this effect was abolished when lipids where added after neurospheres has begun to grow, suggesting an effect on the neurosphere-initiating NSCs specifically. We are currently teasing out the cellular and molecular mechanisms by which lipids alter NSC behaviour using in vitro and in vivo strategies.

2-C-96 Huntingtin-associated protein 40: Interaction and toxicity in Huntington's disease

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Huntington's disease is an autosomal dominant neurodegenerative disorder caused by an expansion of a polyglutamine tract in exon 1 of the huntingtin protein. The polyglutamine expansion is thought to contribute to disease by altering protein-protein interactions that occur between huntingtin and various interacting partners. Huntingtin-associated protein 40 (HAP40) is known to interact with the central or carboxyl-terminal portion of huntingtin. When mutant huntingtin is present, HAP40 protein levels are increased and a complex is formed between huntingtin, HAP40 and active Rab5 on the early endosome interfering with early endosomal motility. The objective of this research is to determine the interaction domain between HAP40 and huntingtin allowing exploration of methods to prevent this interaction and to determine if there is toxicity associated with increased levels of HAP40. Fluorescent microscopy was used to determine potential interactions through co-localization between carboxyl terminal huntingtin fragments and HAP40. Biochemical methods, such as immunoprecipitation, were then used to verify potential interactions. HAP40 cellular toxicity was analyzed using a vector containing an internal ribosomal entry site, allowing translation of HAP40 and a marker protein from a single mRNA. This was expressed in an HD cell line and was

analyzed using flow cytometry. Preliminary results show that HAP40 associates with amino acids 2570 to 2700 of huntingtin and that elevated levels of HAP40 increases cellular toxicity.

2-C-97 The Interactome at the N17 Region of Huntingtin

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Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by a polyglutamine expansion in the huntingtin protein. Recent research demonstrates that post-translational modifications of huntingtin could be an important determinant of mutant huntingtin's toxicity in HD and is therefore of interest when studying huntingtin's function. Of particular interest are the first 17 amino acids at the amino terminus of huntingtin (N17), where phosphorylation at specific residues have shown to be critical modulators of mutant huntingtin's toxicity and localization within neurons. To uncover a mechanism through which phosphorylation mediates toxicity at N17, this project will aim to study how phosphorylation within N17 alters the interactome at this site. With the use of affinity chromatography columns using N17 synthetic peptides, 14-3-3 zeta and beta (and others) have been identified as possible interactors. Through the use of bio-molecular assays and cell imaging techniques, we have discovered that the binding of these 14-3-3 isoforms might not be phospho-specific. In light of the relevance of N17's phosphorylation on toxicity within HD, uncovering a mechanism through which 14-3-3's and other N17 specific interactors bind to huntingtin and the study of how these interactors could be mediated through phosphorylation could help elucidate possible mechanisms through which huntingtin is regulated via phosphorylation in neuronal cells and dysregulated in HD.

2-C-98 Early presynaptic and glial functional changes at the neuromuscular junction of an ALS mouse model

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the progressive loss of motoneurons. The first event observed in the pathology is the loss of the neuromuscular junction (NMJ), which occurs before symptoms onset. Evidence from ALS mice models show that glial cells play a key role in disease progression. However, the role of Perisynaptic Schwann cells (PSCs), glial cells at the NMJ, is unknown in ALS. In normal conditions, they maintain NMJ's organization, decode synaptic activity and modulate plasticity. We hypothesized that PSC properties are altered early in the disease. Using immunohistochemistry, Ca2 imaging and electrophysiological recordings of synaptic transmission, we characterized the NMJ of the SOD1G37R (SOD) mice and their wild-type (WT) littermate at a presymptomatic stage on Soleus (SOL) and Sternomastoid (SM) nerve-muscle preparations. While there were no morphological changes at the NMJ at P120, PSC Ca2 responses evoked by 50 Hz nerve stimulation were enhanced in slow motor-units (SOL) and decreased in fast-fatigable ones (SM). Electrophysiological recordings on the SOL showed that SOD synapses had a larger quantal content than WT with higher spontaneous activity in type IIa fibers. There was no difference in depression and short-term plasticity between SOD and WT synapses. Together, these results suggest that PSC excitability and synaptic properties are modified long before symptoms onset. The motor-unit type specific changes in PSC behavior reported here could be linked to the selective vulnerability of NMJ types in ALS.

2-C-99 Alterations in the metabolism of nerve growth factor cause retrograde alterations in the basal forebrain cholinergic neurons

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Nerve growth factor (NGF) is a target-derived neurotrophin necessary for the phenotypic maintenance of the adult basal forebrain cholinergic system. NGF is released in the extracellular space as a precursor (proNGF) along with the proteases necessary for its maturation and degradation. Following release, proNGF is cleaved to mature NGF (mNGF) by plasmin, and the unbound mNGF is rapidly degraded by MMP9. In Alzheimer's disease (AD), a degeneration of the cholinergic system contributes to cognitive impairments, coincident with molecular changes the NGF metabolic cascade leading to the accumulation of proNGF. We have previously demonstrated that a chronic inhibition of plasmin in the cerebral cortex of rats is sufficient to induce a reduction in mNGF, an accumulation of proNGF and a degeneration of the local cholinergic synapses. We recently performed a similar experiment where we chronically infused plasmin's endogenous inhibitor (α2antiplasmin) along with a retrograde marker to induce the same molecular changes and to label projecting cholinergic neurons. By using quantitative laser scanning microscopy, we quantified the size of the cholinergic cell bodies and the expression of key proteins central to the cholinergic phenotype. We demonstrated that alterations in the metabolism of NGF in the target tissue (cerebral cortex) are sufficient to induce retrograde changes in cholinergic neurons, indicative of a pre-degenerative state. Our data strongly supports that alterations in NGF's extracellular metabolism lead to the cholinergic degeneration seen in AD.

2-C-100 Is white blood cell count a key determinant of stroke severity and clinical outcomes after acute ischemic stroke?

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Introduction: We hypothesized that higher degrees of leukocytosis is a marker of worse clinical outcomes and prognosis after acute ischemic stroke. Methods: This retrospective study included data from Phase 3 of the Registry of the Canadian Stroke Network on consecutive patients with ischemic stroke who were admitted to one stroke center in Ontario and one center in Nova Scotia. We included all consecutive patients admitted to hospital with ischemic stroke from July/2003 to March/2008. We excluded patients taking corticosteroids, anti-epileptic drugs, or antibiotics; and patients with cancer, renal dialysis or liver cirrhosis; and pregnant patients. Results: Higher white blood cell count (WBC) is significantly associated with greater degree of impairment ($p<0.0001$), greater degree of disability ($p=0.0005$), higher risk of a Total Anterior Circulation Stroke ($p<0.0001$) and higher 30-day mortality ($p<0.0001$) after adjustment for major potential confounders. The Kaplan-Meier curves indicate that abnormal WBC is associated with higher mortality after acute ischemic stroke ($p=0.001$). However, there was no significant association between WBC and length of stay in the acute stroke care center ($p=0.9877$). Conclusions: Our study suggests that a higher WBC on the initial admission an acute ischemic stroke is associated with poorer prognosis regarding the degree of impairment and disability, risk of further ischemic stroke and 30-day mortality. The length of stay in the acute stroke care center was not adversely affected by WBC on admission.

2-C-101 Diet-Induced Obesity Disrupts Hippocampal Synaptic Plasticity and May Alter NMDA Receptor Subunit Expression in Female Animals

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Purpose: Obesity has begun to be associated with impairments in cognitive function; however, the underlying cellular mechanisms are poorly understood. Our aim was to confirm an effect of diet-induced obesity upon hippocampal synaptic activity, and to then examine protein-related changes. Methods: Female rats were fed either a control diet (CD; 10% kcal from fat), or a high-fat

diet (HFD; 45% kcal from fat) for 16 wks. Body weight, food consumption, and fasting blood glucose levels were monitored. Upon sacrifice brain, liver, adrenal glands, and fat pads were harvested. Synaptic transmission and plasticity (i.e., LTP) were examined in the hippocampal CA1 sub-field by recording field potentials from acutely prepared slices. The distribution of NMDA receptor subunits was examined by using either cell-surface biotinylation, or differential filtration-centrifugation followed by immunoblotting. Results: The HFD animals had significantly heavier fat pads and greater problems handling a glucose load. Basal synaptic transmission was similar between groups, but HFD rats displayed a moderate, albeit significant, reduction in the magnitude of LTP. As well, the number of CD slices that met threshold potentiation for LTP (20% increase over baseline) was significantly greater. Preliminary analyses suggest that surface expression of the GluN1 subunit was reduced in hippocampus of HFD animals. Conclusions: The feeding protocol induced an obese phenotype in female rats, moderately impaired hippocampal synaptic plasticity, and may have reduced surface expression of the GluN1 subunit.

2-C-102 Spatial and temporal interactions and properties of activated microglia and reactive astrocytes during the development of Alzheimer's-like symptomatology in an Alzheimer's mouse model

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Microglia and astrocytes have the ability to adopt a specialized 'activated' or 'reactive' state when exposed to adverse brain conditions. In Alzheimer's disease (AD), activated microglia and reactive astrocytes are detected around senile plaques. However, how these cells contribute to the onset or progression of AD still remains an open question. We investigated the properties of these cell types in the CRND8 transgenic AD mouse model by applying confocal imaging and WB analysis. Our results show complex spatio-temporal changes in the interaction of microglia and astrocytes around Aβ plaques during the progression of AD. We found that subtle rearrangements of microglial morphology and astrocyte reactivity were detected as early as 1 month when Aβ plaque deposition is absent. By 2-3 months, low numbers of activated microglia and reactive astrocytes begin to surround small Aβ deposits. The establishment of complex reactive glial domains (RGDs) can be observed at 4 months, when amoeboid microglia fully encompass large Aβ plaques and become surrounded by reactive astrocytes forming an elaborate outer shell-like structure. Intriguingly, after 6 months, the domains become progressively disrupted. We also observed gradated inflammatory phenotypes of glial cells. These are first restricted to RGDs but spread locally in late stages. We conclude that communication between microglia and astrocytes may be a key process in the ability of the brain to surmount a reparative response to early neurodegenerative conditions but may be disrupted or become overwhelmed in later stages of AD.

2-D-103 Cortical interactions between the rostral and caudal forelimb areas in the rat

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INTRODUCTION: Corticocortical interactions between motor areas are not well understood. In the sensorimotor cortex of rats, intracortical microstimulation shows two distinct cortical areas that produce forelimb movement: a caudal forelimb area (CFA, the equivalent of the primary motor cortex (M1) in rats), and a rostral forelimb area (RFA, a putative premotor area). In this project, we studied how RFA affects the corticospinal outputs of the CFA. METHODS: We used a paired pulse paradigm in which one stimulating electrode is implanted in RFA, and the other in CFA. A sub-threshold conditioning stimulus was delivered in the RFA prior to a moderately supra-threshold test stimulus delivered in CFA. In different trials, the

timing between the pair of stimuli (interstimuli interval or ISI) was varied from 0, 2.5, 5, 10 to 15 msec. Motor evoked potentials (MEPs) were recorded from palmaris longus, extensor digitorum, biceps brachii, and triceps brachii using implanted microwires and standard electromyography techniques. Data from a total of 19 pairs of RFA/CFA sites were collected in 4 rats. RESULTS: At shorter ISI the stimuli always elicited larger MEP responses than the test stimuli alone, showing a short-latency facilitory influence of the RFA on CFA outputs. At longer ISI, some sites produced facilitation and others suppression of the CFA outputs. CONCLUSION: The effects of RFA on CFA are similar to the ones described between the ventral premotor cortex and M1 in the macaque monkey (Prabhu, et al. 2009), supporting the hypothesis that RFA acts as a premotor area in the rat.

D – Sensory and Motor Systems

2-D-104 Computational Modeling of 3-D Head-Free Gaze-Shift Control

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Shifting the line of sight allows us to place selected visual objects in retinal regions specialized for processing different features. This shift is naturally implemented by coordinated movement of eye and head. We are proposing an analytical framework based on the rotational kinematics underlying the three-dimensional head-free gaze shifts. Then, we train a three-layer feedforward neural network based on the tested results of our kinematic model. Input layer consists of representations of three signals: retinal error, initial head-in-space orientation and initial eye-in-head orientation. Eye-in-head and head-in-space rotations required for implementation of the gaze shift and foveation of the desired target are represented in the output layer while the hidden layer comprises the units which transform the input signals into output signals. We analyze the frames of reference and position dependencies of the hidden units to understand the underlying mechanisms they use to implement the reference frame transformations. Varying the coding scheme of the outputs amongst different physiological possibilities, we try to test their effects on signal processing in the network.

2-D-105 Magnocellular and Parvocellular FMRI-Activation in Separate Subdivisions of the Human Lateral Geniculate Nucleus

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Visual information from the retina to the brain is transmitted along the magno-cellular (M) and parvo-cellular (P) pathways. In this fMRI study, we exploited the distinct spatial, temporal, and chromatic characteristics of visual stimuli that drive each of these two systems in order to functionally map how they are laid out in the human dorsal lateral geniculate nucleus (LGNd). The study consisted of two experiments. The first defined the LGNd functionally using a standard retinotopic procedure while the second used a saw-tooth design to vary the spatial, temporal, and chromatic properties of a grating stimulus. The grating stimulus started off as an isoluminant red / green grating with a maximal contrast, a spatial frequency of 2 degrees per cycle, and a temporal frequency of 2 Hz. This grating stimulus changed in incremental steps to one that had two shades of gray with a Michelson contrast of 10%, a spatial frequency of 0.2 degrees per cycle, and a temporal frequency of 15 Hz. Fourier analyses on the fMRI data were used to create phase maps. The resulting phase maps for Experiment 1 confirmed the well-established retinotopic organization of the human LGNd while the resulting phase maps for Experiment 2 showed that the more ventral and medial portions of the LGNd responded more to M-stimulation while the more dorsal and lateral portions of the LGNd responded more to P-stimulation. These spatial patterns of fMRI responses in the human LGNd seem to be consistent with the known spatial

arrangement of the M and P layers that others have identified in the monkey LGNd.

2-D-106 Mechanical hypersensitivity in mice lacking class I MHC molecules

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Growing evidence support the idea that class I MHC molecules are expressed in neurons of the central nervous system (CNS). While their function has been associated with synaptic refinement in the visual cortex and long term potentiation in the hippocampus, their role in other areas of the CNS remain poorly understood. In this study, we report the expression of class I MHC molecules predominantly on inhibitory interneurons of the spinal cord dorsal horn. Interestingly, knockout mice lacking surface expression of class I MHC molecules have a distinct loss of parvalbumin-expressing inhibitory interneurons. This loss is associated with mechanical hypersensitivity and enhanced nocifensive behaviors in the formalin test. These data indicate that class I MHC molecules play an important role in the viability of dorsal horn parvalbumin inhibitory neurons.

2-D-107 Reference frames for grasping movements: an fMRI repetition suppression study

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FMRI research on reaching suggests that the parietofrontal network flexibly processes information, switching between gaze-centered coordinates for visually-guided reaches and body-centered coordinates for proprioceptive reaches (Bernier et al. 2010). The neural circuits encoding coordinates for grasp-goals have not been explored yet. We used a 3T fast-event related fMRI adaptation design to investigate this question. Right-handed subjects grasped a visible 3D object or their unseen left hand resting on an apparatus placed in front of them while fixating one of three fixation points. At the beginning of each trial, an auditory cue informed subjects whether to grasp the target to the left or to the right of the body midline. A variable delay of 4-7 s was followed by a go cue. Coordinates of the grasp-goals varied relative to Gaze (left, right) and Body (left, right) in successive trials, yielding a 2 (visual vs. somesthetic target modality) x 2 (gaze vs. body coordinates) x 2 (repeat vs. novel trial) design. We analyzed the adaptation occurring during the preparatory phase of the movement. We found that pIPS encodes location of visual targets in coordinates linked to both gaze and body, while somesthetic targets are represented in body-centered coordinates. In addition, visual and somesthetic target location is represented in body-centered coordinates in areas dPM, LH aIPS and pIPS. These findings suggest that the relative contribution of gaze and body-centered coordinates for representation of grasp-goals location is contingent upon the sensory modality of the target.

2-D-108 Persistent inward currents are modulated by inhibitory inputs in humans, but these estimates are contaminated by other motor neuron properties

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Background: Motor units (MU) receive diffuse monoaminergic input that increases motor neuron gain by increasing persistent inward current (PIC). This neuromodulatory input biases motor output toward coactivation of agonist and antagonist muscles. Thus, it has been proposed that agonist-antagonist coordination relies on focused inhibitory inputs that adjust motor neuron gain by reducing PIC in appropriate MU pools. Reciprocal inhibition moderates PIC amplitude in a decerebrate cat model, but this has not been demonstrated in humans. Methods: PIC amplitude was estimated via paired motor unit analysis of human soleus MUs,

and inhibitory input was modulated by passively placing the ankle in neutral, plantarflexion, and dorsiflexion. Reciprocal inhibition was assessed by stimulating the nerve to the antagonist (common peroneal nerve) and plotting post-stimulus time histograms of soleus motor unit spike delays. Additionally, PIC amplitude was estimated during ramp contractions that varied in plateau duration and rate of rise to account for other motor neuron properties (spike threshold accommodation (STA) and spike frequency adaptation (SFA)) that could contaminate estimates of PIC derived from paired motor unit recordings. Results: As predicted, PIC estimates tended to be higher in dorsiflexion, when reciprocal inhibition was reduced. Estimates of PIC amplitude increased by 44.5% with the longest ramp durations and slowest rates of rise ($F(2,26)=4.25$, $p=0.025$). This suggests that estimates from paired motor unit recordings are contaminated by STA and SFA.

2-D-109 The impact of motion stimulus variability on the temporal dynamics of a target selection task

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Random-dot stimuli with coherent motion in opposite directions have been widely used in sensorimotor decision-making research. Data suggest a process whereby a hypothetical "neuron/anti-neuron" pair each accumulate a signal about the net difference in evidence for and against their preferred choice and race to a decision bound. However, the random-dot stimuli used in most studies only contain coherent motion in one of the two directions and therefore cannot directly test the neuron/anti-neuron hypothesis. We tested the neuron/anti-neuron model by pairing different amounts of coherent motion signals in two opposite directions against a background of dots moving in Brownian motion. Two types of stimuli were used. In the "narrow-coherence" (NC) set, the vector component in the coherent direction replaced the background Brownian motion of the coherent dots. In the "Brownian-drift" (BD) set, the coherent vector component was added to their Brownian motion. For each set, 52 different combinations of net and base coherences were used, ranging from (0%/0%) to (64%/32%) of dots moving in each direction. RTs and success rates in the BD and NC set were primarily driven by the net coherent motion, but the RTs for low net coherent-motion stimuli (0 - 8%) also tended to decrease as the base coherence (i.e., total motion energy) increased. Analysis of the motion stimuli and diffusion model simulations suggest that this latter effect could be explained at least in part by the instantaneous signal-dependent variability of the dot stimuli presented, and thus has a peripheral origin.

2-D-110 Characterizing the arrival of task-relevance: Parametric delays in a rapid reaching task reveal the transition from salience-based to task-based performance

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When people are required to make low-latency reaches toward an array of potential targets (with the final target cued only after movement onset), initial trajectories resemble the 'global effect' observed in low-latency saccades when multiple targets or distractors are present. That is, the initial trajectories resemble an average of trajectories toward the potential targets on the screen. Past work with this paradigm has demonstrated that reaches under these conditions are sensitive to the spatial location of targets, the number of targets on each respective side of space (up to a limit of 4), and the recent history of the reaches. Recently, we demonstrated that trajectories deviate toward high-salience (i.e., high luminance) targets, even when there are twice as many targets (and therefore twice the likelihood of the final target appearing) on the opposite side of space, and that this dominating effect of salience disappears after a 500 ms pre-cue period (Wood et al., 2011, JOV). In the present study, subjects performed a similar task

(i.e., targets with salience differences), but there were 10 incremental pre-cue delay conditions. This manipulation allowed us to characterize in detail the function describing the transition from a fast, salience-modulated processing pathway to a slower, task-relevant pathway.

2-D-111 Dorsolateral prefrontal cortex deactivation and saccade-related local field potential activity in the superior colliculus

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Cognitive control requires the selection and maintenance of task-relevant stimulus-response associations, or rules. The dorsolateral prefrontal cortex (DLPFC) has been implicated by lesion, functional imaging, and neurophysiological studies to be involved in representing rules and modulating other brain structures to execute the appropriate task. However, the mechanisms by which the DLPFC interacts with other structures are poorly understood. Here, the functional relationship of the DLPFC with the superior colliculus (SC) was investigated in monkeys performing an interleaved pro- and anti-saccade task. The DLPFC was deactivated bilaterally while the local field potentials (LFPs) of neuronal groups in the SC were recorded. LFP power in the theta (5-8 Hz), alpha (8-13 Hz), and low beta (13-20 Hz) frequency bands was lower after stimulus onset for saccades into the response field of neuronal groups versus the mirror location. Power in these same frequency bands after stimulus onset was higher for anti-saccades than pro-saccades. Deactivation of the DLPFC did not affect stimulus onset related LFP activity, but reduced high beta (20-30 Hz) power in the preparatory period for both pro-saccades and anti-saccades. These results are consistent with the idea that DLPFC exerts an excitatory influence on the SC and suggest that communication between the DLPFC and SC is mediated by beta oscillations.

2-D-112 Proprioceptive recalibration and reach adaptation after training with altered terminal feedback of the hand

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When reaching with continuous, misaligned visual feedback of the hand, reaches are adapted and proprioceptive sense of hand position is recalibrated to partially match the visual feedback provided. It is unclear if similar adjustments arise after reaching with terminal visual feedback, when there are shorter temporal intervals for participants to experience current visual and proprioceptive feedback. Here, participants reached to a target with either continuous or terminal visual feedback that was gradually rotated 30° clockwise with respect to the hand. Subjects then completed two additional blocks of trials with the 30° rotated cursor. Reach adaptation (aftereffects) and proprioceptive recalibration were similar in magnitude across all three training blocks when continuous visual feedback was available. In particular, subjects recalibrated their movements by 16° and shifted their felt hand position by 7° leftwards. In contrast, reach adaptation was smaller when terminal visual feedback was provided and proprioceptive recalibration increased across training blocks with terminal visual feedback, such that by the end of the third block of trials, proprioceptive recalibration was similar in magnitude to proprioceptive recalibration achieved by the continuous visual feedback training group. Thus, despite the absence of continuous visual feedback, participants demonstrated motor learning and recalibrated their sense of felt hand position with terminal feedback, although more slowly than with continuous feedback.

2-D-113 Evidence for independent control of the visuomotor mapping for the planning and rapid online correction of reaching movements

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During visually-guided reaching, the motor system (MS) presumably uses visuomotor mappings

between current arm and target location to plan and initiate the proper response to the target. It also has feedback circuits that inform the MS of the state of the limb and the environment. If any unexpected changes in the environment occur after reach onset, the MS can recruit these circuits, such as the "rapid online correction mechanism" (rOCM), to correct the unfolding movement. It is still not clear if the mapping circuits for planning and online correction are shared or independent. Two recent studies in which subjects corrected for target displacements while reaching under either a visuomotor inversion or mirror transformation yielded contradictory evidence. We did a long-term study in which subjects made reaching movements in either a mirror or inversion transformation. We presented rare "probe" trials, in which the target jumped 10° CW or CCW to assess the state of adaptation of the rOCM compared to that of the initial voluntary reaching response. Our results suggest that after extensive practice of a visuomotor transformation, subjects readily adapted their planning of the initial reach direction, but failed to adapt their rOCM. Instead, subjects seemed to suppress or diminish the gain of the normal rOCM response in the direction of the visual target displacement, while applying a late appropriate mirror or inversion correction. Our findings are consistent with the hypothesis of independent visuomotor mapping circuits for reach planning and online correction.

2-D-114 Differences in motor encoding of head unrestrained gaze shifts in reactive vs. volitional saccades in the primate Superior Colliculus

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Recently, using a memory guided saccade paradigm, we presented data that suggest that motor activities of visuomotor and motor neurons in the superior colliculus(SC) use different coding schemes, target relative to the eye and gaze displacement vectors respectively(Sadeh et al.Soc.Neurosci. Abstr, 2012). Here we asked if the motor coding of these two classes of neurons differs in different behavioral tasks. We recorded neurons in head unrestrained monkeys during memory guided, reactive: stimulus appears simultaneously with GO signal which is extinguishing of the fixation light, and volitional gaze shifts: subjects are free to choose from an array of targets available all at once. 3D eye and head rotations were recorded, and receptive field data were analyzed in multiple frames using a statistical method reported previously (Keith et al. J. Neurosci. Meth. 2009). To date 62 neurons were recorded from the left and right SC of two monkeys. 18 of these only showed a visual response, 14 neurons had a motor response and the remainder showed visual (after target presentation) motor (around the gaze saccade) responses. Here we focused on the analysis of spatial coding of motor burst in visuomotor and motor neurons. So far we have analyzed the motor activity of 7 motor and 7 visuomotor neurons. Taken together the motor activity in reactive saccade tends to fit the target relative to eye model the best and gaze displacement vector in the volitional saccades. These preliminary data suggest that SC neurons can utilize different codes depending on the nature of the task.

2-D-115 Treatment Of Upper Limb Tremor In Patients With Parkinson Disease Or Essential Tremor Using Botulinum Neurotoxin Type A And Kinematic Assessment

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Treatment of Essential Tremor (ET) and tremor in Parkinson Disease (PD) has not been possible due to the difficulties of clinically assessing the complexity of multi-joint tremor through traditional visual observations. The injection of Botulinum neurotoxin type A (BoNT-A) has been considered in the past but results were not as successful. This study demonstrates the efficacy of Xeomin® by use of kinematic measurement to deconstruct tremor at multiple joints, thereby providing a comprehensive assessment of ET and PD tremor.

Patients are assessed over 6 months using 3D accelerometer, electrogoniometers and a torsiometer to measure tremors at the wrist, elbow, and shoulder. Kinematic information was used to determine injection sites while clinician experience determined the dosage. The kinematic and clinical tremor rating scale was conducted during each visit. 6 weeks after the first injection the total tremors for shoulder, elbow and wrist was reduced in PD patients by 31%, 39%, and 53%; and also in ET patients by 23%, 16%, and 47%, respectively. The rest tremor UPDRS score for item 20 had decreased over 16 weeks from 2.75 to 1.81 for PD and 0.66 to 0.28 for ET. Likewise for action tremor, item 21, there was a decrease from 1.67 to 0.77 for PD and 2.88 to 1.42 for ET. This clinical trial showed a reduction in the overall arm tremors post BoNT-A injection and improvement in patient outlook. The use of the kinematic device and software helped to deconstruct the complex movements of tremors which would be otherwise not possible through visual inspection.

2-D-116 Transient pupil dilation is evoked by salient visual stimulation and SC microstimulation

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The appearance of a salient stimulus in the environment initiates a multi-component orienting reflex to prepare the body for quick, appropriate action. The components include a shift of gaze and attention, as well as changes in heart rate and pupil dynamics. It is hypothesized that the superior colliculus (SC) coordinates this orienting response. Many studies have found a significant influence of stimulus saliency on shifts in gaze and attention, and have causally implicated the SC in the process. However, the effect of saliency modulation and the role of the SC on other components of orienting, such as transient pupil dilation, are less understood. While requiring monkeys to keep their gaze fixed, we either presented a salient visual stimulus or delivered weak electrical microstimulation to the intermediate SC layers (saccades were not evoked). Results showed similar transient pupil dilation was elicited after either visual or electrical stimulation, and critically, dilation onset latency was 50 ms later for visual stimulation, suggesting the SC is a physiologically likely candidate to coordinate the transient dilation as part of the orienting response. We further manipulated visual saliency using different levels of visual stimulus contrast. The size of evoked pupil dilation scaled with the level of saliency, with a larger dilation observed for the more salient stimulus. Together, the results suggest that transient pupil dilation, as one component of orienting, is modulated by stimulus saliency and the SC is a likely neural substrate.

2-D-117 Spatiotemporal property of visual response in the Superior Colliculus: Comparison of single unit activity and local field potentials

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Local field potentials (LFPs) are neurophysiological signals that can be recorded simultaneously with conventional single unit activity. Single unit activity (SUA) represents the output signal of the neuron. In contrast, LFPs are thought to represent the sum of activity of neighboring synapses, reflecting the population activity of nearby neurons, including their synaptic inputs from other brain regions and local neural networks. In this study, we simultaneously recorded single unit activity and LFPs from the monkey Superior Colliculus (SC) and compared the spatial and temporal properties of these two signals. We successfully recorded 35 pairs of SUA and LFPs from 2 monkeys. The onset latencies of the visual response were not significantly different between SUA and LFP (68±6 ms for SUA, 69±5 ms for LFPs). However, the duration of the visual response was longer for LFPs than SUA (104±43 ms for SUA, 164±63 ms for LFPs, $p < 0.001$). Response fields (full width at half maximum of the visual response on SC map, Marino et al., 2008) of the signal tended to be larger for LFPs than SUA (0.9±0.3 mm for SUA, 1.1±0.4 mm for LFPs, $p < 0.01$). Interestingly, 43 % of LFPs (15/35) showed significant inhibitory response after

the phasic visual response, which was not visible in SUA. This might reflect inhibitory inputs from the basal ganglia and/or the local inhibitory network in the SC. Overall, the results suggest that LFPs provide qualitatively different information than single unit activity, which will help in better understanding the local processing and visuomotor function of the SC.

2-D-118 Mechanosensitive ion channel candidates involved in osteoarthritis pain

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Joint pain is the most prominent symptom of arthritis, a disease affecting 4.2 million Canadians. Osteoarthritis (OA) pain manifests itself as a mechanical hypersensitivity to innocuous stimuli such as joint movement and palpation. Whether this mechanical hypersensitivity is the result of a general increased excitability of nociceptors or a sensitization of the mechanotransduction process is currently unresolved. In sensory neurons, mechanotransduction occurs through mechanosensitive (MS) ion channels that convert physical forces into electrical signals. While single channel recordings have proven their existence, their molecular identity has remained elusive. Our previous work identified several transmembrane proteins that may act as candidate MS ion channels. In this study, we demonstrate that these candidate MS ion channels are expressed in sensory neurons and that their expression is increased in a mouse model of OA associated with mechanical hypersensitivity. Furthermore, single channel analysis of these candidates expressed in vitro indicates they are involved in cellular mechanosensitivity. These candidate MS channels may be involved in mechanical hypersensitivity in vivo, thus making them potential attractive therapeutic targets in the treatment of OA pain.

2-D-119 Sensory deprivation alters properties of short- and long-term plasticity in the rat central auditory system

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Sensory deprivation affects synaptic plasticity in multiple ways. Here, both long-term and short-term plasticity were assessed in rats reared in unaltered acoustic conditions and those reared in continuous white noise (WN) from postnatal day (PD) 5 to PD 50-60 (i.e., subjected to patterned sound deprivation). In anesthetized (urethane) rats, field postsynaptic potentials (fPSPs) in the primary auditory cortex (A1) were elicited by stimulation of the medial geniculate nucleus (MGN). Theta-burst stimulation (TBS) of the MGN elicited greater levels of long-term potentiation (LTP) in sensory-deprived (WN exposed) animals relative to controls. Additionally, paired pulse (PP, inter-stimulus intervals from 25-1000 ms) responses were examined in both groups before and after LTP induction. Control animals showed PP depression (i.e., a smaller, second fPSP) prior to TBS, which remained unchanged following LTP induction, suggesting a postsynaptic locus of LTP. Interestingly, rats reared in WN exhibited very little PP depression prior to LTP induction, but demonstrated levels of PP depression that were not statistically different from controls after LTP induction, indicative of a selective involvement of presynaptic LTP mechanisms in sensory-deprived animals. Importantly, LTP induction appeared to reverse the deprivation-related abnormalities of plasticity properties following sensory deprivation. Together, these experiments demonstrate the ability of sensory experience to alter plasticity of both short- and long-term thalamocortical synaptic responses.

2-D-120 Neural correlations code for stimulus contrast

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Natural sensory stimuli are characterized by time varying moments such as mean (first-order) and

variance (second-order). While psychophysical studies have shown that second order attributes are critical for perception, how they are encoded in the brain remains largely unknown. Here we focused on second-order feature coding by correlated activity. We recorded from two example sensory systems that share many similarities: the primate vestibular system and the fish electrosensory system. Peripheral sensory neurons in both systems respond to amplitude modulated noise stimuli (Fig. 1A.1, B.1). We found that the correlation coefficient between spike trains coded second order attributes (i.e. envelope, Figs. 1A.2, B.2) whereas single neuron firing rate coded first order attributes (Fig. 1A.3, B.3). We built a simple phenomenological mathematical model based on the leaky integrate-and-fire formalism that reproduced our experimental data (Fig. 1C.1, C.2) and predicted that optimal coding of second-order stimulus features by correlation is achieved for non-zero values of baseline variability as quantified by the coefficient of variation (CV) (Fig. 1C.3). We tested this prediction by plotting our data as a function of CV and found that our model could explain variations on both vestibular and electrosensory data (Fig. 1D). Our results show that correlated activity codes for stimulus attributes that are distinct from those coded by firing rate and provide a novel role for neural variability. Such codes are predicted to be a general feature of sensory processing.

2-D-121 Motor cortical neurons classified with joint loads during posture predict muscle activation patterns in a reaching task

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Our ability to perform accurate movements depends on precisely timed patterns of muscle activation. While the exact spatiotemporal patterns can only be generated at the spinal level, it is unclear how much primary motor cortex (MI) contributes to these details of motor output. This study examines this issue by first classifying neurons to muscle groups in one task (postural load response), and then examining whether these pools of neurons can predict the spatiotemporal patterns of each respective muscle group during a dynamic task (visually-guided reaching). For the first task, we recorded the activity of M1 cells (N=540) and shoulder and elbow muscles (120 EMG recordings) from non-human primates (N=5) during a postural task when loads were applied to the shoulder and/or elbow. Muscles displayed characteristic load preferences which approximately reflected their anatomical action (e.g. elbow-flexor muscles). Cells with significant load relation (N=379) were assigned to a neuron pool (e.g. elbow-flexor cells) if their load preference was within 22° of a muscle group's load preference. During the visually-guided reaching task, each muscle group displayed specific temporal patterns of activation for each movement direction, with characteristic timing shifts. Correspondingly, each neuron pool displayed similar spatiotemporal patterns of activity. Our results suggest that M1 participates in generating the necessary spatiotemporal patterns of muscle activity that produce voluntary motor actions.

2-D-122 Short-term changes in motor cortical excitability following cTBS and motor training in individuals with stroke

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Following middle cerebral artery stroke, motor and sensory deficits are common. Understanding how stroke alters interhemispheric interactions is required to design rehabilitation techniques. In individuals with stroke we compared motor cortical excitability prior to and following continuous theta burst stimulation (cTBS) over the contralesional primary motor cortex (M1), primary sensory cortex (S1), or sham stimulation. We hypothesized that following M1 stimulation, M1 excitability would decrease in the contralesional hemisphere and increase in the ipsilesional hemisphere, while S1 or

sham stimulation would have no effect on M1 excitability. 23 individuals in the chronic stage (>6 months) of recovery from ischemic stroke were randomized to receive one of the 3 forms of stimulation. Each performed a motor task that required moving a computer mouse to a target, using the hemiparetic arm. Transcranial magnetic stimulation (TMS) based recruitment curves (RC) were generated bilaterally using 6 intensities before and after cTBS over M1, S1 or sham stimulation+task practice. RCs were performed 10 and 30 minutes post-cTBS. Two, 2-way ANOVAs (Stim Type X Time) were run at 145% active motor threshold (dependent measure). Both hemispheres demonstrate an interaction effect (ipsilesional: F=3.845, p=0.01, contralesional: F=5.661, p=0.001). cTBS over S1 had the largest impact on M1 excitability (increased ipsilesional; decreased contralesional). Our data demonstrate that contralesional S1 can alter ipsilesional M1 excitability and suggest S1 may be a target for interventional TMS.

2-D-123 Investigation of the reference frames for translational self-motion encoded in the rostral fastigial nucleus for vertical plane head reorientation

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The vestibular sensors provide self-motion information in a head-centered reference frame. However, to contribute appropriately to tasks such as reaching, vestibular signals must be transformed from a head- to a body-centered reference frame. Previous studies provided evidence for a transformation of vestibular signals towards body-centered coordinates by demonstrating shifts in the spatial tuning properties of rostral fastigial nuclei (rFN) neurons when the head was statically repositioned relative to the body in the horizontal plane (i.e., yaw reorientation). Importantly, however, if rFN cells reflect a true transformation of vestibular signals into a body-centered reference frame in three-dimensions (3D), then their responses should also exhibit head-orientation-dependent tuning when the head is statically reoriented in the vertical plane (i.e., pitch/roll reorientation). We tested this hypothesis by characterizing the spatial tuning of rFN neurons in a rhesus monkey during sinusoidal translational motion (0.5 Hz, /-9 cm, /-0.09G) with the head upright and when tilted in pitch or roll. To date, observed tuning shifts towards body-centered coordinates for vertical plane head reorientation were much smaller than those previously reported for head reorientation in the horizontal plane, such that cell activities were more consistent with encoding a head-centered representation of motion. These results, while preliminary, call into question the idea that rFN cells reflect a true transformation of vestibular signals into body-centered coordinates in 3D.

2-D-124 The effects of the monoamine oxidase inhibitor PLZ and its active metabolite PEH on nociceptive behaviours in male versus female mice

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Different anti-depressants have been shown to have analgesic properties through their effects on the levels of monoamines such as serotonin (5-HT) and norepinephrine (NE). The present study explored the effects of the monoamine oxidase inhibitor Phenelzine (PLZ) and its active metabolite Phenylethylidenehydrazine (PEH) on nociceptive behaviours in the formalin test, a model of tonic nociception in male and female mice. PLZ significantly elevates levels of 5-HT and NE but also inhibits the enzyme GABA-transaminase leading to surges in GABA levels in the nervous system. In contrast, PEH only inhibits GABA-transaminase, increasing GABA levels, but does not affect 5-HT or NE levels. We find that systemic treatment with PLZ or PEH prior to formalin injection could significantly attenuate nociceptive behaviours in the second phase of the formalin response. While both male and female mice had an overall reduction in second phase nociceptive behaviours in the PLZ and PEH

treated groups, the analgesic effect of the drugs was greater in male mice. Using high performance liquid chromatography (HPLC) and immunohistochemistry, we have also determined the relative influence of the affected neurotransmitter systems (5HT, NE and GABA) between male and female mice treated with PLZ and PEH. These findings are the first to examine the analgesic properties of PLZ and PEH in an acute pain model and the associated sex differences in the responses to these treatments.

2-D-125 Effects of somatic inputs on interhemispheric inhibition

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Motor output may be modulated via a mechanism called interhemispheric inhibition (IHI) in which one motor cortex (M1) inhibits the contralateral M1. This mechanism may be probed using a paired pulse TMS protocol in which a conditioning pulse (CS) is applied to one hemisphere immediately prior to a second test pulse (TS) applied to the opposite hemisphere, resulting in decreased motor output. Changes in neural excitability within somatosensory cortices modulate IHI though it is unclear whether somatic input originating from the periphery modulates IHI. This is an important question to be probed as somatic inputs are integral in guiding hand movement. In this study, IHI will be investigated in right-handed individuals using a paired pulse TMS protocol. IHI will be tested at weak and strong levels of inhibition in which the CS pulse is of a lower intensity than (weak) or equal to (strong) the TS. To test the effects of somatic inputs on IHI either the median or digital nerve will be electrically stimulated prior to the TMS pulses. The arrival of somatic input at the cortex will be timed to synchronize with either the CS or TS pulse to evaluate the effects of somatic inputs on IHI. Further, nerve stimulation will be delivered at two intensities to probe intensity dependent effects on IHI. Based on previous work, it is hypothesized that an intensity dependent relationship between the CS and somatic input will exist, with strong inputs eliciting reductions in IHI when paired with a strong CS, while weak or strong inputs will elicit reductions in IHI when paired with a weak CS.

2-D-126 Cholinergic system activation paired with repetitive exposure to visual stimulus induces cortical plasticity mediated by modulation of GABAergic interneurons

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Cholinergic system modulates selective properties of neurons (e.g. orientation and spatial frequency selectivity) during cortical plasticity. A behavioral study has shown that pairing cholinergic and visual stimulation induced an improvement of the visual acuity on a specific pattern. Here, we studied the interaction of this visual enhancement with GABAergic system. We recorded field potential in the primary visual cortex of anesthetized rat during visual stimulation (converting sinusoidal pattern). The visual exposure was performed on restrained awaken rats during 10min/day for 7 days and cholinergic system was stimulated through an electrode implanted in the basal forebrain or by injecting the cholinesterase inhibitor donepezil (i.p., 0.5mg/kg). Muscimol, a GABAA agonist, was infused through a pre-implanted cannula (i.c.). The difference of pre- and post-exposition signal/noise ratios (SNR) value was used to compare between groups. SNR were averaged for the different orientations and spatial frequencies. VEPs were enhanced in the cholinergic system stimulated groups (1.84±0.94, 1.74±1, Mann-Whitney p=0.01 and p=0.046) compared to control group (0.11±0.44). In addition, muscimol completely blocked the increase of SNR (0.15±0.45, p=0.94). Our study demonstrates that repeated visual exposure paired with cholinergic stimulation induces increase of cortical response and can be abolished by GABA activation. This indicates that cholinergic-dependent plasticity is dependent on GABAergic system and that cholinergic pathway could have an important role during visual learning.

2-D-127 Regeneration of axons through autologous bridges placed between an intact donor tibial (TIB) nerve and a recipient denervated common peroneal (CP) nerve counteracts the negative effects of delayed nerve surgery in Sprague Dawley rats

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Does insertion of autologous nerve grafts to bridge between an intact donor nerve and a recipient denervated nerve stump 1) lead to axon outgrowth from the donor into the denervated distal nerve stump, 2) promote axon growth within the stump both proximal and distal to the bridges and 3) 'protect' the distal stump to improve axon regeneration after delayed nerve repair? First, we placed three 4mm CP nerve bridges (excised from the contralateral hindlimb) aseptically between intact tibial (TIB) and denervated CP nerves (Fig B) and used retrograde labeling to count TIB neurons that regenerated axons across the bridges into the 3m chronically denervated CP nerve. We found that ~10% of TIB neurons regenerated axons across the bridges and in both directions within the chronically denervated CP nerve. Second, in rats in which bridges were (experimental) and were not (control) placed, either counts of neurons that regenerated their axons (after retrograde dye injection) or had reinnervated muscle (motor unit counting using contractile force measurements: Fig.B) were made 5m after delayed (4m) surgical repair of the transected CP nerve. The nerve regeneration and number of motor units in the reinnervated muscles were significantly increased when the chronically denervated CP nerve was 'protected' by regenerating nerves from the donor TIB nerve. Hence donor nerves contributing axons to chronically denervated nerves 'protect' resident Schwann cells to improve regeneration and functional recovery, a technique with promise to improve clinical outcomes after devastating nerve injuries.

2-D-128 Neuroplasticity induced by transcranial direct current stimulation over the motor cortex and the dorsolateral prefrontal cortex in older healthy subjects

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Learning and memory difficulties occur in aging and neurodegenerative diseases. Noninvasive brain stimulation methods are useful tools to study cortical neuroplastic changes, which might at least partially form the basis of these alterations. The objective of this study was to determine the influence of the dorsolateral prefontal cortex (DLPFC) on M1 excitability. We studied neuroplasticity in 6 healthy older subjects (mean age 59 /-4) with anodal transcranial direct current stimulation (tDCS) over M1 and anodal and sham tDCS over DLPFC for 13 minutes at 2mA. Motor evoked potentials, intracortical facilitation (ICF) and short-interval intracortical inhibition (SICI) within M1 and the connection from DLPFC to M1 at different interstimulus intervals were measured with transcranial magnetic stimulation. A significant increase of excitability occurred at 30 and 75 minutes after anodal tDCS over M1. There was no significant effect change in SICI or ICF. M1 conditioning stimulation of DLPFC led to a trend towards inhibition at 8-10ms and at 40ms at rest. At 40ms, the inhibition was reversed to facilitation after anodal but not after sham tDCS Increased M1 excitability after anodal motor cortex tDCS could be demonstrated in this older population. These changes lasted up to 75 minutes after stimulation with 2mA. Inhibitory effects of DLPFC stimulation on M1 excitability at interstimulus intervals of 8-10ms are likely due to a direct connection between these areas. At a longer time interval of 40ms, the inhibition may be mediated via structures such as the thalamus.

2-D-129 Spatiotemporal Evolution of the Response Field of Frontal Eye Field Neurons During Memory Delay Period

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Many neurons in the Frontal Eye Field (FEF), particularly visuomovement neurons, exhibit memory delay activity during memory-guided gaze shift, in which subjects make delayed gaze movements to cued locations in space. However, the nature of the information coded in this delay period is not fully understood. Recent findings in our lab suggest that the visual and movement activity of FEF neurons in rhesus macaques, at both individual and population level, encodes target location and final gaze position respectively. (Sajad et al. Society for Neuroscience Abstract, 2013). This suggests a visual-to-motor transformations occurring within single visuomovement neurons between the time of target presentation and gaze movement. In this investigation we are asking what spatial information is contained in the delay activity, and whether this activity is involved in visual-to-motor transformations observed in these visuomovement cells. Preliminary analysis of the spatiotemporal evolution of the response field for 15 visuomovement cells reveals that there is a progressive transition from target location coding to gaze movement coding during the delay period. This suggests that during the memory interval, these visuomovement cells are not just retaining target location information, but they are actively transforming information from a sensory representation into a motor representation.

2-D-130 Role Of Early Visual Cortex In Transsaccadic Perception Of Visual Feature Memory In Humans

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Visual processing is partially suppressed during a saccade and useful visual information is limited to discrete fixations, yet we are able to perceive the world with persistent spatiotemporal continuity. Transsaccadic perception (TSP) is the process by which visual feature information held in visual short term memory (VSTM) is integrated across saccades to maintain spatial stability. Our lab has recently confirmed that VSTM can be disrupted via transcranial magnetic stimulation (TMS) over the parietal and frontal eye fields. However, the mechanisms of VSTM storage are not clear. Early visual cortex (EVC) has also been shown to be involved in VSTM and spatial updating, so we have proposed it could play a role in TSP of low-level visual features. In this experiment, participants were required to discriminate orientation change in a Gabor patch across a memory interval during fixation or across saccade that either maintained the stimulus within the same hemifield or changed its location from one hemifield to another. TMS was applied over retinotopically-defined regions of the right and left EVC (as determined via functional localizer), corresponding to the bottom-right and bottom-left quadrants of the visual field. TMS results from 9 subjects revealed a moderate negative hemifield specific effect of TMS, especially when the stimulus was presented at greater eccentricities. Overall, these findings may implicate a role of the EVC for TSP and VSTM but we are currently retesting our subjects with a higher visual memory load (two stimuli) to see if this yields stronger TMS results.

2-D-131 Articulatory phonatory coupling in people who stutter

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People who stutter (PWS) are at the lower end a speech motor skill continuum related to the control of inter-system sensory-motor coupling. This study examines the effect of jaw perturbations on the laryngeal system in PWS and matched controls, with the hypothesis that aberrant sensory-motor coupling in PWS becomes more evident when control parameters are altered. Five male adult PWS and five matched controls participated. Participants reiterated [bapi] at habitual and fast speech rates under 2 conditions: jaw-free (JF), and

with a bite-block (BB). Using PRAAT, jitter and shimmer (vocal fold perturbation indices) were extracted for the vowel [a]. Results show a significant Group x Condition interaction ($p<0.05$) for jitter and a Group x Speech rate interaction ($p<0.01$) for shimmer. For jitter, controls showed significant increases in the BB condition relative to JF across rates. Shimmer values increased significantly only for controls in the habitual rate condition. These findings show that voicing of normal speakers is more perturbed by the bite-block than that of PWS. Normal speakers have a highly integrated dynamic sensory-motor relationship between jaw/tongue and voicing, but the oral motor structures of PWS are less tightly coupled together. The biteblock, by fixing one component of the oral motor system, benefits PWS because it reduces coordination complexity for them, but disadvantages controls as it interrupts normally integrated coordination. Such disruptions could trickle down to the phonatory system, given its close neuro-anatomical link to oral structures.

2-D-132 Spinal dI3 interneurons provide a source of sensory drive during locomotion

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We have previously shown that glutamatergic spinal dI3 interneurons (dI3 INs) form disynaptic circuits linking low-threshold mechanoreceptors and motoneurons, and that they are critical to regulating grip strength. Activation of spinal cutaneous-motor pathways is able to drive locomotor recovery following spinal cord injury in rodents. dI3 INs may be involved in this locomotor recovery. A first step to determining their involvement is to establish whether dI3 INs and the sensory-motor circuit they mediate are involved in locomotor activity in the uninjured animal In-vitro recordings of lumbar dI3 INs during drug-induced locomotion in hemisected spinal cords showed that lumbar dI3 INs are rhythmically inhibited during locomotion. We then eliminated dI3 IN neurotransmission by conditionally knocking out vGluT2 in dI3 INs. These mice showed deficits in generating locomotion by stimulation of cutaneous nerves in neonatal isolated spinal cords. We next studied these mice during treadmill walking. Both control and mutant mice were able to walk up to speeds of 80 cm/s. Analysis of paw placement and limb kinematics revealed that removing dI3 IN output does not compromise the basic rhythm and pattern of locomotion. However, differences in joint angle and stance duration suggest a loss of weight support during stance. These results show that dI3 INs provide a source of sensory-evoked drive that contributes to the generation of normal locomotor activity.

2-D-133 Contribution of Nav1.8 in starburst amacrine cells to electroretinogram oscillatory potentials

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Oscillations (OPs) in the electroretinogram (ERG) of 50-150 Hz fall into the same frequency range as oscillations transmitted from retinal ganglion cells (RGC) to higher visual centers. The circuitry that generates these oscillations in the retina is elusive but interactions in the inner retina seem important. An atypical TTX-resistant voltage gated sodium (Nav) channel, Nav1.8, is restricted to starburst amacrine cells (SAC) and a subset of RGCs, both of which are known to generate membrane oscillations in response to light. We assessed the contribution of Nav1.8 to light-evoked retinal oscillations (>50 Hz) recorded in vivo to a range of flash energies in dark and light adapted conditions, by using the Nav1.8 blocker, A803467 The amplitude and implicit time of the a- and b-waves were not significantly changed after Nav1.8 was blocked. This supports the previous data showing Nav1.8 is found only in SAC and a subset of RGCs. We found that Nav1.8 contributed little to the initial OPs (OPs 1&2), significantly decreased the middle 4 OPs (OPs 3-6), most strongly in response to mesopic flash energies and had no effect on OP7. The timing and frequency of the OPs was unchanged after Nav1.8 was blocked. Nav1.8 is

localized to RGCs therefore we used optic nerve transection (ONTX) to determine whether RGCs contributed to the OPs. ONTX had no effect on OPs suggesting both that high frequency oscillations in RGCs seen by other groups do not strongly contribute to OPs and that Nav1.8 in SACs is a contributor to the OPs particularly in response to lower energy stimuli.

E – Homeostatic Neuroendoctrine Systems

2-E-134 Stress-induced dynamic changes in amygdalar endocannabinoid signaling depend on CRH-R1

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Corticotrophin releasing hormone (CRH) and endocannabinoid molecules (eCBs) are neuromodulators influencing how the brain perceives and responds to stress. CRH activation of the R1 receptor (CRH-R1) acts throughout the brain and pituitary to facilitate endocrine and behavioral stress responses, while activation of the endocannabinoid CB1 receptor has an opposite effect on these outputs. Although these receptors have overlapping distribution, few studies have investigated if these neurotransmitter systems are capable of interacting. Using adult male Sprague Dawley rats, we have found that icv administration of CRH decreases eCB levels (anandamide) in the amygdala at 10 and 30 min post CRH injection. Interestingly, at both time-points we also observed an increase in amygdalar levels of the eCB degradative enzyme fatty acid amide hydrolase (FAAH). Subsequent tests using agonist and antagonist approaches revealed these effects are mediated by CRH-R1 activation and not CRH-R2. Further, we have also reproduced these findings using restraint as a novel stressor, and are currently examining these outputs in transgenic mice. Thus, it appears CRH-R1 activation reduces the tonic inhibitory influence normally exerted by anandamide by increasing its breakdown within the amygdala. These data also provide new evidence to suggest that FAAH activity can be dynamically modulated via the CRH-R1 signaling pathway.

2-E-135 Elucidating the roles of TCAP-1 on glucose transport and skeletal muscle physiology

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Teneurin C-terminal associated peptide (TCAP) is a cleavable bioactive peptide on the carboxy terminus of teneurin proteins. TCAP plays a fundamental role in the cellular stress response and metabolism. Previous studies show that, in vitro, TCAP-1 interacts with the dystroglycan complex to activate MEK-ERK1/2 and PI3K/AKT pathway signalling systems in neurons to stimulate cytoskeletal reorganization. Further, TCAP-1 administration also results in increased ATP production, decreased lactate accumulation and increased glucose transporter relocation to the plasma membrane. These findings indicate that the primary role of TCAP may be to regulate metabolic optimization in the brain by increasing the efficiency of glucose transport and energy utilization. Given that the dystroglycan complex is a key component of the neuromuscular junction and skeletal muscle function, I hypothesize that TCAP-1 plays a significant role in regulating energy metabolism and cellular function in skeletal muscle and acts via a similar mechanism shown in neurons. Within the scope of 4 primary objectives, a research program is presented designed to address this hypothesis. Data obtained so far indicates that TCAP-1 induces 3H-deoxyglucose transport into neurons and skeletal muscle cell models in an insulin-independent manner, the key proteins are expressed in skeletal cells and preliminary data suggests that in vivo TCAP-1 administration results changes in skeletal muscle morphology.

2-E-136 The motivation to obtain sugar pellets is attenuated in the ghrelin receptor knock-out rat

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A role for ghrelin in the motivation to obtain palatable food sources has been supported by many recent studies. In the absence of a negative energy balance, which typically drives food procurement, ghrelin appears able to increase the saliency of palatable food stimuli and increase the amount of work an animal performs to obtain food. Ghrelin acts on the growth hormone secretagogue receptor 1A (GHSR-1A) in the central nervous system to exert its orexigenic effects. We used a recently developed GHSR knock-out (KO) rat to examine the role of ghrelin in the motivation to obtain food reinforcers. Food restricted GHSR-KO and wild-type (WT) rats were trained to bar press on a fixed ratio 1 (FR1) schedule of reinforcement, followed by FR4, and finally a progressive ratio (PR) schedule for purified grain-based pellets. This was repeated for purified chocolate, sugar, and high-fat pellets, respectively. We hypothesized that an absence of intact ghrelin signaling in KO rats would attenuate the amount of effort produced to obtain reinforcers, particularly with highly palatable reinforcers. An analysis of the cost-benefit ratio as measured by breakpoint was conducted. Results show that while the KO and WT rats performed similarly to each other on a PR schedule to obtain grain, chocolate flavor and high-fat chocolate pellets, when pressing for sugar pellets, the KO rats failed to increase their rate of bar pressing. As sugar is known to be very rewarding, these results highlight that the absence of GHSR can influence the incentive value attributed to food rewards.

2-E-137 Neurotrophic actions of TCAP-1: A novel and potent inhibitor of the vertebrate stress pathway.

Louise de Lannoy[1], **Dhan Chand**[1], **Lifang Song**[1], **David Lovejoy**[1]
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The stress response is one of the most evolutionarily conserved survival mechanisms. The Corticotropin Releasing Factor (CRF) family of peptides is an integral part of this mechanism that evolved early in metazoan evolution. The early origin of CRF suggests that it may possess many paralogous genes due to its increased exposure to gene duplication events. In 2004 Qian et al undertook an investigation into possible homologues of CRF using a urocortin probe in rainbow trout and instead uncovered a peptide family located along the C-terminal region of the rainbow trout ortholog of teneurin-3. This peptide family was named the Teneurin C-terminal Associated Peptides (TCAP) and has subsequently been shown to be involved in neuroprotection against stress. Both TCAP and teneurin are involved in neurogenesis however initial studies of the synthetic version of TCAP established that this peptide possesses a number of biological actions independent of teneurin. Recent findings indicate that TCAP-1 is involved in promoting filopodia elongation. This cytoskeletal change is initiated by an interaction between TCAP and β-dystroglycan at the cellular membrane. The above findings suggest that TCAP-1 can function independently from teneurin, however, evidence of how TCAP is processed from its proprotein has not yet been shown. I have shown that TCAP-1 can be transcribed as a smaller mRNA transcript. I have further identified and isolated potential promoter regions upstream of the TCAP-1 region. This work confirms our molecular evidence that TCAP has independent functionality from teneurin.

2-E-138 Brainstem noradrenergic afferents excite hypothalamic neurons through glutamate co-release.

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The paraventricular nucleus of the hypothalamus (PVN) integrates inputs from diverse stress-sensitive brain areas to regulate the hypothalamus-

pituitary-adrenal (HPA) axis. Catecholaminergic (CAergic) neurons in the caudal medulla densely innervate the PVN, release noradrenaline/adrenaline (NA/A), and increase the excitability of parvocellular neuroendocrine cells (PNCs). Interestingly, subpopulations of caudal medulla CAergic neurons also express vesicular glutamate transporter 2, raising a possibility that the excitatory effects of these inputs may also rely on glutamate transmission. To investigate how NA/Aergic afferents signal to PNCs, we used an optogenetic approach. Cre-recombinase-dependent adeno-associated viral vector (AAV) carrying channelrhodopsin 2 (ChR2)-enhanced yellow fluorescent protein (eYFP) was stereotaxically injected into the caudal medulla of mice that expressed Cre under the control of the tyrosine hydroxylase (TH) promoter. We observed that eYFP axons innervating the PVN were TH immunopositive, verifying targeted expression of ChR2-eYFP. Using whole-cell voltage clamp in PNCs (cells held at -70 mV), we observed that blue light stimulation (473 nm, 5 ms) evoked inward postsynaptic currents (PSCs), with short latency (4.3 ± 0.2 ms) and large amplitude (-93 ± 11 pA). In current-clamp, the light stimulation evoked a rapid postsynaptic depolarization, which occasionally triggered single action potentials. The light-evoked PSCs were still evident in the presence of adrenergic receptor antagonists. They were also unaffected by a GABAA receptor antagonist

2-E-139 Neurotrophin receptor TrkB mediates hypoxia-induced responses of adrenal chromaffin cells

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Adrenomedullary chromaffin cells (AMCs) are neurosecretory cells that are activated in response to hypoxic stress and responsible for many resulting physiological responses. Once activated, the AMCs release catecholamines into the circulation that act on target organs. Although this response has been well characterized, the signalling cascades that regulate hypoxia-induced catecholamine release by AMCs remain largely undefined. Our aim was to further elucidate the molecular machinery that governs synaptic plasticity of AMCs during hypoxic stress. Brain-derived neurotrophic factor, a molecule responsible for CNS synaptic adaptations, and its receptor TrkB are expressed in AMCs throughout development. To test whether TrkB activation is involved in hypoxia-induced synaptic release of catecholamines, we applied a TrkB agonist to AMCs exposed to 48 hours of normoxia or hypoxia (2% oxygen) and measured secretion. TrkB activation induced catecholamine release from normoxic AMCs, but had a greater effect on hypoxic cells. The increase in catecholamine secretion by hypoxic cells was due to an increase in both the number of responsive cells and secretion frequency of individual cells. This response was calcium-mediated and could be prevented by tyrosine kinase antagonism. Full-length TrkB was significantly upregulated in hypoxic AMCs and microarray studies on immortalized chromaffin cells suggested its expression is regulated by hypoxia-inducible factor 2. Thus, TrkB receptor activation appears to play a significant role in regulating hypoxia-induced catecholamine release by AMCs.

F – Cognition and Behaviour

2-F-140 The Platelet Activating Factor Pc (O-14:1/2:0) Is Associated With Verbal Memory In Depressed Coronary Artery Disease Patients And Predicts Improvement Due To An Exercise Intervention

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Background: Depressed coronary artery disease (CAD) patients are at risk for dementia, with early deficits in verbal memory often observed. Exercise interventions (EI) can improve memory performance but, not all CAD patients benefit. Platelet activating factors (PAFs) are potent pro-inflammatory lipids implicated in

neurodegeneration. Here, we explored PAFs as potential biomarkers of verbal memory performance and benefit from EI in depressed CAD patients. Methods: 23 CAD patients who met DSM-IV depression criteria were recruited from an EI program. Verbal memory performance was assessed using the California Verbal Learning Test II [CVLT] according to guidelines for vascular cognitive impairment. Plasma PAF concentrations were measured using electrospray ionization mass spectrometry. Results: A greater abundance of the PAF PC (O-14:1/2:0) at baseline was associated with poorer immediate (IVR) and delayed (DVR) verbal recall (IVR: Spearman`s Rho = -0.542, p = 0.008; DVR: -0.440, p = 0.036). Greater PC (O-14:1/2:0) at baseline also predicted improvement in CVLT measures over 12 weeks of EI (IVR: 0.579, p = 0.006; DVR: 0.429, p = 0.052 (trend)). These associations persisted after adjusting for depressive symptoms; however, only IVR and change in IVR remained associated with PC (O-14:1/2:0) after adjusting for age, gender, and cardiopulmonary fitness in independent linear regression models. Conclusions: Preliminary data support the investigation of PC (O-14:1/2:0) as a biomarker of immediate verbal recall and improvement due to EI in depressed CAD patients.

2-F-141 Visceral fat is associated with lower executive functioning in adolescents

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Obesity is associated with lower cognitive performance in children and adults, especially on tasks of executive function. While visceral fat (VF) carries particularly high risk with regards to cardiometabolic health, it is unknown whether it plays a special role in obesity-cognition relationships. In a community-based sample of 983 adolescents (12-18 years old) from the Saguenay Youth Study, VF was quantified using magnetic resonance imaging and total body fat was measured using multifrequency bioimpedance. Cognitive performance was assessed using a battery of neuropsychological tests measuring executive functioning and memory. We found that larger volumes of VF were associated with lower performance on six measures of executive functioning. Further, we found a sex by VF interaction on five measures of executive functioning, such that females with low VF performed better than females with high VF on four of five measures. We observed no such differences between males with low and high VF. The above relationships were present independent of total body fat, while taking into account a number of potential confounders, including age and household income. Our results support previous findings demonstrating an impact of obesity on cognition in adolescents, and suggest that obesity-associated decrements in cognitive performance may be driven by fat deposited viscerally. Further, our results suggest that females may be more sensitive to the negative effects of VF on cognition; VF-cognition relationships might be mediated by different mechanisms in the two sexes.

2-F-142 A new disorder is out there: Assessing Internet addiction

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Internet over-consumption can cause dysfunctional usage resulting in several deleterious outcomes. The "Internet Use Disorder" is gaining importance in diagnostic manuals as its prevalence increases. A factorial structure analysis of tools assessing Internet addiction for adolescents and adults published between January 1993 and October 2011 was performed and a theoretical framework for optimizing tools design was developed. The descriptive properties of 14 questionnaires were measured and the position of the instruments' methodology, validity, reliability and model fit was

presented, along with the preferred factorial analysis method and validation technique. Results indicate some heterogeneity in study methodology and differences in descriptive and dimensional aspects of assessment tools. The three factor categories compulsive Internet use, negative outcomes and salience were central to Internet addiction questionnaires. Furthermore, the social dimension was often under-represented. No significant difference was observed in the distribution of factor categories across Internet addiction questionnaires and DSM-IV-TR and ICD-10 diagnostic criteria for substance dependence. The validity and reliability of the evaluated questionnaires reflect the newness of this field. The under-representation of the social use of Internet is a problematic situation as it is causing considerable damages. Future research should consider that Internet addiction evaluation questionnaires need refinement. Appropriate strategies are proposed (Lortie and Guitton, under revision in Addiction).

2-F-143 Brain networks for semantic and syntactic processing: Converging evidence from MEG and DTI

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Introduction: Language processing depends on a ventral temporal-frontal route supporting semantic information, and a dorsal parietal-frontal pathway subserving syntax and phonology. We mapped the brain regions that generate electrophysiological responses to semantic and syntactic anomalies using Magnetoencephalography (MEG), testing whether these responses are generated in dissociable pathways, with the corresponding dorsal and ventral white matter (WM) tracks identified using diffusion tensor imaging (DTI). Methods: Semantic anomalies were created by substituting the final word of a sentence with an unexpected completion and syntactic anomalies were elicited by introducing a grammatical error in the verb tense or agreement. Participants performed a sentence acceptability judgement task. Results: Oscillatory changes in MEG event related synchronization/desynchronization (ERS/ERD) in alpha and beta frequency bands were localized using beamforming. ERD in the 8 to 30 Hz frequency band was observed in temporal-frontal regions for both semantic and syntactic anomalies. Additionally, syntactic anomalies engaged bilateral dorsal parietal and precentral areas. The power decreases for semantic and syntactic violations proceeded along the cortical regions overlying dorsal and ventral WM pathways. Conclusions: Responses to semantic and syntactic anomalies were localized to cortical regions within ventral and dorsal language networks. 8-30 Hz ERD may reflect neural activity throughout language networks connected by major white matter tracts.

2-F-144 Inhibition of glycogen synthase kinase 3 in the dorsal striatum impairs the learning of a complex motor task

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Glycogen synthase kinase 3 (GSK3) has been recognized to play a role in mediating long-term depression, an important mechanism for memory consolidation. However, the role of GSK3 in learning is still at its infancy. We investigated levels of phospho-GSK3 in different brain regions as well as the effects of GSK3 inhibition during motor learning in mice. Performances of mice on accelerating rotarod were evaluated during 4 consecutive days. Mice showed a rapid improvement in performance within the first training day whereas at the second day, their scores improved slowly and reached a plateau at the third day. Western blot analysis reveals that levels of phospho-GSK3 were increased in the striatum at day 2 whereas they were decreased in the hippocampus at day 1. No change was observed in the anterior cortex and cerebellum. Intracranial injections of the GSK3 inhibitor SB216763 in the dorsal striatum were performed before each rotarod session. We observed that blockade of GSK3 activity dose dependently impaired rotarod performances at day 3 and 4. To verify whether

reduced performances were due to impaired motor capacities, we performed the stepping, wire suspension and pole tests on these mice. Moreover, we injected SB216763 in an independent group of mice on the fifth day after they fully learned the rotarod task. These tests revealed that the drug has no effect on motor execution and abilities. Results suggest that striatal GSK3 activity is more associated with the improvements in motor performances during the learning of a motor task than the control of motor activity.

2-F-145 Which Psychosocial Factors Predict Weight Loss Outcomes after Bariatric Surgery in Morbidly Obese Patients?

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Introduction: Morbid obesity is defined as having a body mass index (BMI) of greater than 40kg/m². At present, bariatric surgery is the most effective treatment available for long-term weight management. However, not all patients undergoing bariatric surgery are successful. We proposed that individuals with a higher pre-operative BMI, higher levels of depression, low self-esteem, and a history of childhood sexual abuse (CSA) will be more likely to have poor outcomes 1-year after Roux-en-y-gastric bypass as evidenced by a BMI > 35 kg/m². Methods: We administered the Beck Depression Inventory-II, Rosenberg Self-Esteem Scale and a self-report measure assessing history of sexual abuse, to 271 bariatric surgery candidates at St. Joseph's Healthcare Hamilton. Patients completed the questionnaires prior to surgery and at 1-year post-surgery. Results: Depression and self-esteem scores were within normal range in the follow-up sample (n=47) and 12% of participants reported a history of CSA (n=46). On average, patients achieved a good weight loss outcome at 1 year (BMI = 32.5 kg/m²). We found that pre-operative BMI accounted for a significant proportion of variance in postoperative weight loss (R^2=.71, $p < .01$), whereas depression, self-esteem and history of CSA accounted for a total of 3% in predicting weight loss. Pre-operative BMI also significantly predicted BMI at 1 year ($\beta = .84$, $p < .001$). None of the psychosocial variables significantly predicted post-operative weight loss. Conclusion: Future studies are needed to target post-surgery intervention.

2-F-146 Ventral tegmental area Beta-2* nAChRs on dopamine and GABA neurons separately mediate nicotine aversion and reward

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Several reports suggest that the neurotransmitter dopamine mediates drug reward and that other non-dopaminergic neural substrates are responsible for the negative motivational effects experienced after drug use. Nicotine produces both rewarding and aversive motivational effects by activating nicotinic acetylcholine receptor (nAChR) subunits located on the dopaminergic and γ-amino-butyric acid (GABA) neurons in the ventral tegmental area (VTA) of the brain reward system. Here we show that Beta-2* nAChRs on dopamine neurons mediate the aversive motivational effects while Beta-2* nAChRs on GABA neurons mediate the rewarding motivational effects of acute nicotine in the VTA. We utilized a lentiviral vector-mediated selective reintroduction of the Beta-2* nAChRs into VTA dopamine or GABA neurons in constitutive Beta-2 knockout mice to double dissociate the conditioned place aversions and preferences for nicotine in nondependent mice. We conclude that the two main neuronal populations in the VTA (GABA and dopamine neurons) respectively signal acute nicotine reward and aversion. These results lead to a better understanding of the neurobiology of nicotine motivation and thus may lead to improved therapeutic treatments for smoking cessation.

2-F-147 Processing of Affective Faces Varying in Valence and Intensity in Shy Adults: An Event-related fMRI Study

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Recent behavioral and electrocortical studies have found that shy and socially anxious adults are hypersensitive to the processing of negative and ambiguous facial emotions. We attempted to extend these findings by examining the neural correlates of affective face processing in shy adults using an event-related fMRI design. We presented pairs of faces that varied in affective valence and intensity. The faces were morphed to alter the degree of intensity of the emotional expressive faces. Twenty-four (12 shy and 12 non-shy) young adult participants then made same/different judgments to these faces while in an MR scanner. We found that shy adults exhibited greater neural activation across a distinct range of brain regions to pairs of faces expressing negative emotions, moderate levels of emotional intensity, and emotional faces that were incongruent with one another. In contrast, non-shy individuals exhibited greater neural activation across a distinct range of brain regions to pairs of faces expressing positive emotions, low levels of emotional intensity, and emotional faces that were congruent with one another. Findings suggest that there may be neural correlate differences for shy relative to non-shy individuals when viewing affective faces that varied in valence, intensity, and discrepancy.

2-F-148 Event-Related Potential and Evoked Power Indices of Sensory Gating in Healthy Controls Stratified into Low, Medium and High Suppressor Groups

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Objectives: Sensory gating is the ability to filter out extraneous information in the environment, and is typically measured in an event-related potential (ERP) P50 gating paradigm as the suppressed response to the second (S2) of two identical paired (S1, S2) clicks. Although the finding of sensory gating impairments in schizophrenia is robust, there is a substantial amount of variability in both schizophrenia patients and healthy controls. Thus, the study of varying P50 gating measures in subsets of healthy participants may provide translational insight into deficits in those with the disorder Methods: Event-related potential (ERP) and evoked power (EP) indices of sensory gating were assessed in low, medium and high suppressor groups (n = 20 per group) of healthy participants Results: With respect to P50 amplitudes, group differences were found for dP50 and rP50, as well as for S1 but not S2. While high suppressors showed greater gamma EP to S1 than both medium and low suppressors, significant group differences for S2 were only found between high and medium suppressors. Beta EP differentiated high and low suppressors for S1 only Significance: Our results suggest that individual differences in gating function may result from initial stimulus processing and encoding more so than subsequent stimulus filtering.

2-F-149 The influence of crowding on grip scaling during grasping

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In this study, we aimed to examine how nearby objects influence our actions towards the target. A white disk of either 3 cm or 3.75 cm in diameter was presented along the horizontal meridian at an eccentricity of 30¢ª either in isolation (uncrowded) or surrounded by six disks with different sizes (crowded). At the beginning of each trial, LCD goggles worn by the participants were closed. Participants held down the start button with their thumb and index fingers pinched together. After the disks had been placed on the table, the goggles were opened. On perceptual trials, participants were required to manually indicate the size of the target disk using their thumb and index finger, and after that to pick up the disk. On grasping trials, participants were required to grasp the target disk with their thumb and index finger as quickly and

accurately as possible. On some trials, the goggles were closed as soon as the start button was released (open loop) so that participants could not see their hands or the disks during the execution of the movement. On other trials, the goggles were closed 3 s after participants released the button (closed loop), permitting a full view of the moving hand and the target. In all tasks, the distance between the index finger and thumb was measured with OPTOTRAK. Even though participants could not indicate the size of the targets on perceptual trials, they scaled their grip aperture to the size of the target on grasping trials. Overall, these findings support the dissociation between vision-for-action and vision-for-perception.

2-F-150 Long-term cognitive outcomes of pediatric epilepsy surgery

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PURPOSE: Little is known about long-term cognitive outcomes after pediatric epilepsy surgery. The few studies addressing this issue have largely focused on IQ alone and yielded contradictory results. It is possible that with increasing time after surgery, neural plasticity could allow for improvements in cognition.This study examined various cognitive measures prior to and following surgery in patients with intractable epilepsy and in a comparison group of nonsurgical epilepsy patients assessed at comparable times. METHOD: 40 participants were tested; 25 had undergone surgery on average 7.7 years ago.They completed IQ, verbal memory, and academic tests.The two groups did not differ on age, age at seizure onset, sex, or number of antiepileptic drugs (AED). RESULTS: IQ and academic skills were similar in both groups at baseline and at follow up. IQ improvement was associated with a lower baseline IQ and was not associated with current AED use or seizure status. Improved math scores were associated with current seizure freedom.Verbal memory declined in both groups, although cessation of AED use was associated with some improvement. CONCLUSION: These results show similar cognitive outcomes in both groups. Changes in IQ and academic skills were not specific to the surgical group and remained stable over time. Declines in verbal memory were found irrespective of the group. Current AED use and seizure status predicted some aspects of cognition in both groups. Surgery itself does not appear to be associated with long-term cognitive changes. Funded by The Ontario Brain Institute

2-F-151 Long-term follow-up of emotional functioning after pediatric epilepsy surgery

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PURPOSE: Children with epilepsy have elevated rates of depression and anxiety. Selected cases benefit from surgery to improve seizure control. Few studies have investigated the possibility of neural plasticity after surgery with respect to affective symptoms. This study investigated emotional outcomes 4 to 11 years after surgery in surgical patients with intractable epilepsy and in a comparison group of nonsurgical patients with epilepsy METHOD: 47 participants were tested; 31 had undergone surgery on average 7 years ago. Patients completed questionnaires assessing anxiety and depressive symptoms. The groups did not differ on handedness, sex, age at seizure onset, current age, or number of anti-epileptic drugs RESULTS: State anxiety was significantly higher in the comparison group relative to the surgical group. The groups were similar in other measures of anxiety and depression. The number of patients who were at risk for meeting the clinical range for anxiety and depressive symptoms was similar for each group. Patients who had seizures within the past 12 months were at risk for meeting the clinical cut-off for depressive problems CONCLUSION: The results show a similar pattern of emotional outcomes for both groups, with the exception of state anxiety. Surgery per se did not appear to have an effect, but the presence of seizures was a risk

factor for clinically significant levels of depression
Funded by the Ontario Brain Institute.

2-F-152 Plastic changes in the dorsolateral striatum underlie responding for rewards: Behavioural, electrophysiology, and optogenetic approaches

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The dorsal striatum is a key substrate for decision making, playing a critical role in the initiation of actions. Medium spiny neurons (MSNs) in the dorsal striatum receive input from multiple cortical regions and project outward via the direct and indirect pathways. Because of the heterogeneity of cortical projections to the striatum, only a small fraction of synapses may encode a particular behaviour, rendering the study of these mechanisms opaque to traditional electrophysiology or anatomical approaches. Recent advances in viral-mediated molecular expression provide elegant methods to target specific synapses within the dorsal striatum. We found that selective inactivation of projections from the motor cortices to the striatum can impair action selection in mice. We then performed patch-clamp electrophysiology in the dorsal striatum of trained mice to examine learning-dependent plasticity in MSNs at motor cortex-striatal synapses. Specifically, we used the light-activated cation channel Channelrhodopsin-2 (ChR2) to activate motor cortex axons and found that the same critical synapses are strengthened after training. Importantly, these effects were selective to neurons projecting to the direct pathway. Finally, we used ChR2 to activate cortical inputs to the dorsolateral striatum while mice were responding for reward. Taken together, these results point to a discrete cortical-striatal circuit that importantly contributes to the learned selection of actions.

2-F-153 Circadian regulation of memory retrieval by BMAL1

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bHLH-PAS transcription factor BMAL1 has been shown to play essential roles in circadian transcriptional rhythm. Importantly, BMAL1 ubiquitously expresses in the brain and other peripheral tissues, thereby regulating circadian transcription rhythms in not only the SCN but also other cells including neurons in the forebrain. In this study, we have tried to understand roles of BMAL1 in the forebrain in learning and memory. To do this, we have derived conditional mutant mice that enable to induce the inhibition of BMAL1 function in the forebrain by regulating expression of a dominant negative mutant of BMAL1 (BMAL1 R91A; dnBMAL1; Hosoda et al, 2004). Biochemical analyses showed that dnBMAL1 mice exhibit disruptions of circadian expression cycle of BAML1-target genes in the forebrain, but not in the hypothalamus. In addition, dnBMAL1 mice displayed normal circadian rhythms at the behavioral level. These results indicated that inhibition of BMAL1 activity forebrain-specifically impairs circadian transcription rhythms without affecting behavioral circadian rhythms. Behavioral analyses using social recognition, novel object recognition and contextual fear conditioning tasks showed that these mutant mice exhibited impairments of memory retrieval tested at ZT10 in a dnBMAL1 expression-dependent manner, while these mutant mice displayed normal memory retrieval tested at ZT4, 16, or 22. These findings indicate that CLOCK/BMAL1 in the forebrain contributes to circadian regulation of memory retrieval.

2-F-154 Unilateral inactivation of the lateral entorhinal cortex but not medial prefrontal cortex impairs memory expression in trace eyeblink conditioning

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Memories of daily experiences initially depend on the hippocampus (HPC) and neocortex; over time

these networks reorganize and become centered on the medial prefrontal cortex (mPFC). The lateral entorhinal cortex (LEC) also plays a role in expressing recently acquired HPC-dependent or remotely acquired mPFC-dependent memory learned through trace eyeblink conditioning (Morrissey et al, 2012). Entorhinal involvement in recent memory expression may be explained by its previously proposed interactions with the HPC. In contrast, it remains unknown how the LEC participates in memory expression after the network disengages from the HPC. The present study tested the possibility that the LEC and mPFC functionally interact during remote memory expression by examining the impact of pharmacological inactivation of the LEC in one hemisphere and the mPFC in the contralateral hemisphere on memory expression in rats. Recent and remote memory expression was significantly impaired after LEC-mPFC inactivation and after unilateral LEC, but not mPFC inactivation. The deficit in memory expression after unilateral LEC inactivation impairs our ability to detect functional interactions between the LEC and mPFC and demonstrates that the integrity of the LEC in both hemispheres is necessary for memory expression. The lack of further significant effect after LEC-mPFC inactivation may be attributable to compensation by other pathways that may include the ventral HPC or perirhinal cortex. Detecting a functional interaction between the LEC and mPFC should therefore be tested with an alternative design.

2-F-155 Psychophysical exploration of the 4th dimension: Event segmentation as a new perspective on time estimation

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An increase in number of changes during an interval is shown to induce time dilation. Different theories try to explain such phenomena from various angles such as attention, predictability, or enhanced information processing. Here we adopt a new perspective, 'event segmentation' as a comprehensive foundation for time estimation, which encompasses other explanations. Event segmentation theory (Zacks, 2007), claims that we perceive the complex influx of information by automatically segmenting an extended interval of time into discrete units, which inherently helps memory consolidation. In order to assess how such theory applies to time perception, we acquired psychophysical data comparing duration judgment of segmented versus un-segmented interval. We used thermal stimulus which was either fixed at 21°C (un-segmented) or fluctuated, going from baseline at 32°C to 21°C three times (segmented). Subjects were asked to either 1) estimate only time or 2) reproduce the temporal dynamic of sensation using electronic Visual Analogue Scale (e-VAS), retrospectively after 15 sec of delay. Our main finding indicates that the duration of segmented interval is remembered better than non-segmented, in accordance with Zacks' theory. Moreover, we show that remembering the dynamics of sensation helped to better remember the total duration compare to remembering only the time dimension. This suggests that changes in sensation might be used as temporal cues to mark the beginning and end of segments and thus help remembering the duration of interval.

2-F-156 Activation of the dopamine D1-D2 receptor heteromer abolishes the acquisition and expression of cocaine-induced conditioned place preference

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Dopamine D1 and D2 receptors form heteromeric complexes in vivo that, upon activation of both receptors, couple to Gq/11 to activate phospholipase C and generate intracellular calcium release. Activation of the D1-D2 heteromer was additionally shown to modulate calcium-calmodulin kinase II phosphorylation and increase brain-derived neurotrophic factor signaling in nucleus accumbens, two processes which have been shown to play an important role in the addictive properties of drugs of abuse. Therefore, the purpose of this

study was to assess the involvement of the D1-D2 heteromer in the regulation of cocaine reward using the conditioned place preference paradigm (CPP). We demonstrated that D1-D2 heteromer activation by the selective agonist SKF 83959 (1.0 mg/kg s.c.) induced place aversion ($p<0.01$), and prevented the acquisition of cocaine (10 mg/kg i.p.) CPP. A single administration of SKF 83959 (2.5mg/kg, s.c.) on the test day was also sufficient to abolish the expression of CPP in cocaine-conditioned animals. Conversely, disruption of the D1-D2 heteromer by an interfering peptide (TAT-D1, 300 nmol, i.c.v.) produced place preference ($p<0.01$) and enhanced the acquisition of cocaine CPP. These findings suggest that the D1-D2 heteromer exerts a tonic inhibitory control over brain reward processes and negatively modulates the perception of cocaine reward. Thus, the D1-D2 dopamine receptor heteromer may serve as a potential therapeutic target for cocaine addiction.

2-F-157 Effect of medial prefrontal rTMS on decision making and dopamine release

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We perturbed medial prefrontal cortex (MePFC) excitability with repetitive transcranial stimulation (rTMS) to investigate its contribution on intertemporal decision making during delay discounting (DD) task. We applied rTMS over the target area to measure MePFC stimulation effect on dopamine (DA) release during [11C]-(+)-PHNO PET. Twenty four healthy volunteers (11 female; 22.1±2.9yr) underwent a behavioral study with DD task under two 10 Hz-rTMS conditions: MePFC and vertex stimulation (control condition). Subsequently, 11 subjects (5 female; 22.2±2.6yr) underwent the same stimulation paradigm (of the MePFC and vertex) during PET. Binding potential (BP) map was generated using the simplified reference tissue model with the cerebellum as a reference in each subject. Statistical analysis was done using SPSS and SPM 2 for behavioral and PET data, respectively. rTMS of the MePFC significantly affected DD task and decreased K-value compared to control stimulation ($t=3.25$, $P<0.01$; student t-test). During the PET study, rTMS on the MePFC (compared to vertex) showed a reduction of BP in the bilateral globus pallidus (GP) and dorsal putamen (DPu) ($P < 0.05$ FDR). The % changes in BP were -11.7±7.8% in the left GP and -14.8±12.5% in the right GP and -9.4±5.1% in the left DPu and -11.0±10.8 % in the right DPu, respectively. The present results demonstrate that rTMS-induced modulation of excitability in the MePFC may affect DD while interfering with synaptic DA level in striatum. This is the first study exploring MePFC and DAergic interaction in a reward circuit in the human brain.

2-F-158 Involvement of the ventromedial prefrontal cortex in representing schemas

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While the ventromedial prefrontal cortex (vmPFC) has been shown to be involved in representing schemas (Kumaran et al., 2009; Tse et al., 2011), the nature of the involvement is unclear. This study tested whether vmPFC lesions would differentially impact activation of a relevant schema and inhibition of an irrelevant one. As vmPFC damage is sufficient to cause confabulation (Gilboa & Moscovitch, 2002), a measure of confabulation was included. Patients and healthy adults made speeded decisions about whether words were closely related to a schema (visiting a doctor). Ten minutes later they repeated the task for a new schema (going to bed) with some words related to the first schema included as lures. The non-confabulating patients performed comparably to healthy adults: high accuracy overall and longer response latencies to reject lures related to the irrelevant schema than lures unrelated to both schemas. Patients with confabulation were less efficient in rejecting irrelevant schema lures. Damage to a vmPFC sub-region--the sub-callosal cingulate cortex--may have in part been responsible for their differing performance, as this region was

spared in the non-confabulating patients. An additional experiment comparing task performance across age corroborated this idea. It had previously been shown that grey matter volume in this region is reduced with age (Mann et al., 2011), and older adults exhibited greater reaction time differences to reject irrelevant schema lures compared to lures unrelated to both schemas, suggesting less efficient inhibition of the irrelevant schema.

2-F-159 Saccadic eye movements and pause/articulation components during a letter naming speed task: children with and without dyslexia

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Naming speed (NS) tasks that measure how quickly and accurately participants can name visual stimuli (e.g., letters), are commonly used to test reading ability. However, the link between NS and reading is poorly understood. Three methods were used to investigate how NS relates to reading and what cognitive processes are involved: (a) changing stimulus composition to emphasize phonological and/or visual aspects (Compton, 2003); (b) decomposing NS times into pause (PT) and articulation (AT) components; and (c) analyzing eye movements during a NS task. We recruited 45 participants across three groups (n=15/group): dyslexics (aged 9, 10), chronological age (CA) controls (age 9, 10), and Reading Level (RL) controls (aged 6, 7). We used a letter NS task and three variants that were either phonologically and/or visually confusing while subjects' eye movements and articulations were recorded. We examined how these four tasks influenced NS performance and eye movements. For all three groups, NS manipulations were associated with specific patterns of behavior and saccadic performance, reflecting differential contributions of NS to reading. The three groups differed significantly in all conditions on NS, AT, PT, and fixation duration (FD). In each case, RL controls were significantly slower than CA controls and had longer and more fixations and saccades, and dyslexics consistently scored in between. Overall, we found that there were clear developmental changes in NS, AT, PT, and FD in normally achieving children from ages 6 to 10 that appear to occur more slowly for dyslexics.

2-F-160 Resting-state functional connectivity dynamics are influenced by network structure

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Neurophysiological and theoretical studies have emphasized the importance of ongoing fluctuations in neuronal systems to support flexible cognitive and behavioral processes. A growing number of functional MRI (fMRI) studies have shown that large-scale brain networks are dynamic, even in the absence of an explicit task. Resting-state functional connectivity (rsFC), when assessed across short and varying time windows, is non-stationary and exhibits spontaneous and recurring patterns. rsFC is known to be constrained by the underlying structural connectivity (SC) and simulations have suggested that this relationship is strongest when FC is derived using long time windows. We empirically examined the influence of SC on FC dynamics by comparing rsFC obtained from anesthetized macaques using BOLD-fMRI to SC derived from macaque axonal tract tracing. In line with previous reports, we observed rsFC fluctuations on the order of seconds to minutes. FC patterns were consistently recapitulated both within and across animals. The correspondence between rsFC and SC increased with increasing rsFC-window size. rsFC was most stable across time for regions with bidirectional SC. Regions with unidirectional SC still exhibited more stable rsFC than regions that were not structurally connected. These data suggest that the transient nature of FC is, in part, dependent on network structure and indicate the dynamic modulation of polysynaptic pathways. Taken together, these results further elucidate how large-scale dynamic functional

coordination exists within a fixed structural architecture.

2-F-161 Optogenetic dissection of the MCH system: implications for sleep-state modulation

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The hypothalamus consists of intermingled inhibitory and excitatory neural circuits. The activity of those circuits correlates with vigilance states, including wake, non-Rapid Eye Movement (REM) sleep or REM sleep. Neurons expressing Melanin-Concentrating Hormone (MCH) have been recently identified as possible sleep-promoting neurons; however, their selective modulation of NREM and REM sleep remain unclear. To investigate the role of MCH neurons modulation of sleep states, we first genetically targeted the expression of excitatory (ChETA) or inhibitory (eNpHR3.0) opsins to MCH neurons and showed that optical stimulations reliably activate or inhibit ChETA and eNpHR3.0-expressing MCH neurons, respectively. Using real-time detection of EEG/EMG, we found that bilateral optogenetic activation of MCH neurons during NREM sleep increased the probability of NREM-to-REM sleep transitions, while MCH neuron activation during REM sleep extended its duration. In contrast, we showed that optogenetic silencing of MCH neurons during REM sleep reduced the amplitude of cortical theta rhythm concomitant to an increase of slower oscillations in the range of (~ 4 Hz). Finally, optical activation of MCH terminals induced fast GABAA-mediated inhibitory currents in local wake-promoting histaminergic (HA) neurons. This inhibitory tone was enhanced by optogenetically-induced MCH peptide release. Collectively, these results support a causal role for MCH neurons in the onset and maintenance of cortical REM sleep in the mammalian brain.

2-F-162 Novel beta alanine analogues attenuate cocaine-seeing behaviour in the rat

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One of the challenges in treating drug addiction is the potential for relapse. Clinical trials with various pharmacotherapeutic agents have historically shown only transient periods of efficacy and unacceptable side effects. There are now many studies relating cocaine addiction to both glutamate and GABA mediated processes, suggesting that an endogenous neurochemical system that permits the "fine-tuning" of both GABAergic and glutamatergic systems may constitute a molecular platform for the design of an anti-craving therapeutic. This proposal investigated a newly developed series of beta-alanine (ß-ala) analogues designed to simultaneously target both GABAergic and glutamatergic transmission. Three ß-ala analogues NC2507, NC2508 and NC2530 were tested for their ability to reduce cocaine self-administration and cue-induced relapse in male Sprague Dawley rats. Dose response curves were established for each of the analogues in rats trained to self-administer cocaine under a progressive ratio schedule. The analogues were also tested for their ability to reduce cue-induced reinstatement in separate groups of rats. Results indicated that while the analogues did not reduce cocaine self-administration when administered alone, combining NC2530 and NC2508 with a subeffective dose of baclofen (1.78 mg/kg) did reduce cocaine reinforced breakpoints. Both NC2507 and NC2530 reduced relapse to cocaine seeking behaviour when administered alone. The data suggest that ß-ala analogues are viable candidates in the pursuit of rational anti-addiction drug design research.

2-F-163 Optogenetic investigation of septal GABAergic modulation of hippocampal theta rhythm.

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Hippocampal neurons oscillate in synchrony at theta (4-10 Hz) frequencies during periods of wakefulness and rapid-eye-movement (REM) sleep, and evidence suggests that these theta rhythms are required for cognitive processing. The hippocampus receives cholinergic, glutamatergic and inhibitory GABAergic inputs from the medial septum (MS), a brain region required for normal theta rhythm generation in vivo. Previous work using lesional, pharmacological or electrical modulation of MS cell activity suggested that septal GABAergic neurons may be important for theta rhythm generation. However, due to the difficulty in achieving both temporal precision in combination with cell-type specificity using these methods, the causality of this neural pathway on hippocampal theta rhythms remains to be clarified. Here, we genetically targeted archaerhodopsin (ArchT), a silencing opsin to GABAergic neurons of the MS. We found that yellow light pulses reliably hyperpolarized ArchT-expressing cells in the MS in brain slices in vitro. Using a combination of optogenetic and electrophysiological (field potential and unit recording) techniques in freely-moving mice, we further found that theta power was significantly and reversibly attenuated when septal GABAergic neurons were optically inhibited during periods of active wakefulness or REM sleep. These results demonstrate that septal GABAergic neurons are critical for normal hippocampal theta rhythm in vivo and may implicate this neuronal population as an important component of cognitive processing mechanisms during wakefulness or REM sleep.

2-F-164 Cognitive effects of alpha-MSH on Alzheimer disease mouse model in multiple behaviour paradigms

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Alzheimers disease (AD) is characterized by the accumulation of beta-amyloid peptide (Aβ), neurofibrillary tangles of hyperphosphorylated tau, dysfunction of the cholinergic system and neuroinflammation. These pathological changes result in the impairment of cognitive functions in AD. Alpha-melanocyte stimulating hormone (α-MSH) is a cleavage product of the pituitary hormone pre-opiomelanocortin. α-MSH exhibits many neuroprotective and anti-inflammatory effects that would be beneficial in treating AD. In addition, α-MSH has been shown to be down-regulated in AD patients. However, the effect of α-MSH in AD has not been investigated. My objective is to determine the neuroprotective effects of α-MSH on the cognition of AD mouse model TgCRND8 mice. TgCRND8 mice and non-Tg littermates were either treated with daily i.p. injections of α-MSH or saline as control. Treatment was initiated when Aβ pathology was well-established in TgCRND8 mice in an attempt to model drug treatment in AD patients. Mice were tested in the Open Field Test and the Y-Maze Test both pre- and post-treatment to examine within subject effects in addition to between-subject global effects. In the spontaneous alternation analysis of the Y-Maze Test, α-MSH rescued the spatial memory in TgCRND8 mice. α-MSH treatment also normalized anxiety levels in the TgCRND8 mice to that of their non-Tg littermates. α-MSH treatment did not affect the locomotion, weight or home cage behaviour in the animals. The mechanism of neuroprotection elicited by α-MSH is to be elucidated.

2-F-165 Behavioural evidence for the role of adult hippocampal neurogenesis in humans: contrasting effects of aerobic exercise and depression inventory scores on pattern separation performance

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Considerable effort has been devoted to unraveling the functional significance of adult neurogenesis in the mammalian dentate gyrus (DG). Our group has proposed that a continual turnover of neurons in the DG could contribute to the development of event-unique memory traces that reduce interference between similar inputs. Here, we

implemented a recognition task containing some objects that are repeated across trials and some objects that are very similar to ones previously observed. The similar objects, termed lures, overlap substantially with previously viewed stimuli, and thus, may require DG neurogenesis in order to avoid interference. Lifestyle factors such as exercise and stress have been shown to enhance and reduce levels of DG neurogenesis in rodents, respectively. Accordingly, we hypothesized that young adults who take part in a chronic exercise regime would demonstrate enhanced performance, whereas those who score high on depression scales would exhibit a selective deficit, at correctly categorizing lures as "similar". Indeed, those who experienced a proportionally large change in fitness demonstrated a significantly greater improvement in their ability to correctly identify lure stimuli as "similar". In contrast, those who scored high on the Beck Depression Inventory were significantly worse than those with relatively lower scores at correctly identifying lures as "similar", while performance on novel and repeated stimuli was identical. Our results support the hypothesis that adult-born neurons in the DG contribute to the orthogonalization of incoming information.

2-F-166 The molecular correlates of multiday memory in an appetitive-conditioning model

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Long-term memory is defined as protein synthesis-dependent memory that lasts weeks, months or years. However, it is now recognized that protein synthesis-dependent long-term memory durations vary widely depending on initial training conditions. In rodent early odor preference learning 24 h protein synthesis-dependent memory occurs after a single trial pairing of the β-adrenoceptor agonist, isoproterenol (unconditioned stimulus), and novel odor (to-be-conditioned stimulus). This 24 h memory depends on an increase in CREB phosphorylation that is maximal 10 min post-training. A 4-day odor preference memory occurs if isoproterenol is paired with phosphodiesterase inhibition and 5-day odor preference memory occurs when histone deacetylation is also inhibited. We investigated CREB phosphorylation post-training in multiday odor preference memory, and found a biphasic increase in pCREB in the olfactory bulb, with peaks at 10 min and 2 h following training, in contrast to the single peak at 10 min in 24 h memory. Histone deacetylation inhibition increased histone acetylation for 0-10 min post training but did not differentiate learning and non-learning controls. Thus, increased histone acetylation, alone, paired with odor, does not produce odor preference memory. These results suggest a biphasic pCREB pattern drives multiday memory in the appetitive conditioning model of early odor preference, a pattern similarly observed with long-term fear memories. The role of later protein synthesis and the targets of the two transcription waves have yet to be identified.

2-F-167 Attentional selection is driven by reinforcement learning during foraging in the macaque

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In contrast with tasks where attention is shifted with a cue, foraging tasks lack external cues, so attentional shifts are internally triggered. These attentional shifts could rely on internal representations that track the value of stimulus features. We identified which choice features are internally encoded and how they are updated. We propose that selection in each trial is explained by competition between values computed for all options available. Two macaques performed a foraging task (>80% rewarded trials) composed of two coloured, drifting gratings that transiently rotated during each trial. To receive reward the monkey needed to attentionally select one stimulus to discriminate the stimulus rotation. Location, rotation direction, and the relative time of rotation were three variables with random reward

associations, varying independently from the rewarded color. We analyzed monkeys' behavior by applying model-free and model-based reinforcement learning (RL). They differed respectively in whether all stimulus features in a trial compete to trigger a choice, or whether only colours compete. Although both RL versions accounted for most of the choices made, only model-free RL predicted the pattern of unrewarded trials. This sub-optimal behavior emerged from local correlations of location and/or rotation with reward that negatively biased attentional selection against the highly valued color. Model-free RL suggests that attentional control emerges from an interaction between feature values operating as inputs and a stochastic covert choice operating as output.

2-F-168 Are visual texture-selective areas recruited during haptic texture discrimination?

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Shape and surface texture provide cues to object identity, both when objects are explored using vision and via touch (haptics). In vision, shape information is processed within the lateral occipital complex (LOC), while surface texture is processed in medial ventro-temporal cortex, in the collateral sulcus (CoS). Evidence indicates that the LOC, despite its location within the ventral visual system, is also consistently recruited during haptic shape processing. We used fMRI to examine whether ventral 'visual' texture-selective areas are similarly recruited when observers discriminate texture via touch. We used a blocked design in which participants attended to sequential pairs of 3-dimensional objects. During each block, the stimuli varied either in their shape or their surface texture (but not both). Participants explored the stimuli using either vision alone or via touch alone in a given run. In vision, the strongest fMRI responses to surface texture (vs shape) perception were observed within medial ventral temporal cortex. When stimuli were explored via touch, the strongest fMRI responses to texture (vs shape) perception were observed dorsally, in the vicinity of secondary somatosensory cortex and inferior frontal cortex. We also observed significant texture-selective fMRI responses in medial ventral temporal cortex within areas analogous to those recruited during visual texture discrimination. Our imaging data demonstrate for the first time that ventromedial temporal areas known to process visual textures are recruited during the perception of surface texture via touch.

2-F-169 Dopamine receptor D2 deficiency reduces mouse pup ultrasonic vocalizations and maternal responsiveness

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Dopamine signalling facilitates motivated behaviours, and the D2 dopamine receptor (D2R) is important for attachment behaviours, including maternal responsiveness. D2R antagonists disrupt maternal behaviour and, in isolated rat pups, reduce ultrasonic vocalizations (USVs) that promote maternal interaction. Here, we examined the effects of genetic D2R signalling deficiency on pup-dam attachment behaviours with Drd2 knockout (D2R KO) mice. Using heterozygous (HET) cross littermates, the effect of pup genotype on isolation-induced USVs was quantified. Independent of parental genotype, D2R-deficient pups emitted fewer USVs than wild type (WT) littermates in a gene dose-dependent manner. Using reciprocal D2R KO-WT crosses, we examined how parental genotype affects pup USVs. HET pups from D2R KO dams produced fewer USVs than HET pups from WT dams. Also, exposure to USV-emitting pups increased plasma prolactin levels in WT dams but not in D2R KO dams, and KO dams showed delayed pup-retrieval and nest-building. These findings indicate the importance of the interaction between pup and dam genotypes in attachment behaviours and further support the role of D2R signalling in maternal care.

2-F-170 Rat 50 kHz vocalizations induced by intra-accumbens injection of dopamine

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It has been postulated that release of dopamine (DA) in the rat nucleus accumbens (NAc) is responsible for the initiation of a positive affective state and emission of 50 kHz appetitive vocalizations. Direct injections of dopaminergic agonists, such as amphetamine or cocaine, into the NAc of rats were shown to induce emission of large numbers of 50 kHz calls, particularly from the shell region. DA, as an endogenous transmitter, has not been directly injected into the NAc. We have hypothesized that direct application of DA into the shell of the NAc would have comparable pharmacological effects to amphetamine, particularly as to the number and subtypes of 50 kHz calls. Fifteen rats were stereotaxically implanted with cannulae in the shell of the NAc. After recovery, animals were injected with 13-20 µg of DA or vehicle in 0.3 µl and their vocalizations were recorded and analyzed by the Avisoft Bioacoustics system. As a positive control, amphetamine (7 µg, 0.3 µl) was also given into the same brain sites. The drugs have induced significantly more flat and frequency-modulated 50 kHz calls as compared to those after saline control. The acoustic parameters of calls and proportion of the flat to frequency-modulated calls was similar after amphetamine and DA. Thus, amphetamine, which is known to release DA from presynaptic terminals in the NAc caused similar pharmacological response to directly injected DA. These results provide further evidence that DA in the shell of the NAc is responsible for the productions of 50 kHz calls. The study was supported by NSERC.

2-F-171 Hippocampal GPER Involvement in Rapid Estrogenic Regulation of Learning

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Estrogens have been shown to affect learning and memory on a rapid time scale through estrogen receptors alpha and beta (Phan et al. 2011, 2012). However, little is known about the rapid effects of the G-protein coupled estrogen receptor (GPER) on learning and memory. G-1 is a selective GPER agonist with a high affinity to GPER. Previously, we have shown that systemic injections of G-1 rapidly improve social recognition, object recognition, and object placement in ovariectomized female mice. The brain regions involved in mediating these effects are still unknown. Recently, it has been shown that microinfusions of 17-beta estradiol into the CA1 of the hippocampus rapidly improve these learning and memory tasks. Our objective is to investigate the effects of GPER in the hippocampus on social recognition, object recognition, and object placement in female mice. G-1 (50, 100, 200, 300, 400 nM) was infused directly into the CA1 of the hippocampus (0.2 µL/min, total volume of 0.5 µL per side). The learning and memory paradigms were developed by Phan et al. (2011) and are completed within 40 minutes of drug administration, therefore focusing on the rapid effects of GPER. Social recognition was improved with the 200 nM G-1 dose and object placement was significantly improved with the 100 nM G-1 dose. The experiment examining the effects of GPER in the hippocampus on object placement is currently underway. Therefore, GPER in the hippocampus may, in part, mediate the rapid, improving effects of estrogens on social recognition and object placement in female mice. Supported by NSERC.

2-F-172 Imagined movements and electroencephalography: Toward the optimization of a motor imagery-based brain-computer interface

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Neuroscientists are working to identify a person's "thoughts" using only neurophysiological measures with devices known as brain-computer interfaces (BCI). This study focused on the development of a BCI motor imagery task that could be used by behaviourally non-responsive patients. Sixteen healthy volunteers completed a motor imagery task while having their electroencephalogram (EEG) recorded. Participants imagined simple and more complex hand movements, and spectral and single-trial analyses were conducted for the bandpower in the mu (7 - 13 Hz) and beta (13 - 30 Hz) frequency bands of the EEG. Comparisons were made for each imagined movement type versus rest using a machine-learning algorithm. For the simple condition, only four participants (25%) produced motor signals for at least one imagined movement type that could be classified significantly from rest (Mean classification accuracy, M = 60.68%, SD = 2.96%). In contrast, eleven participants (69%) produced motor signals for at least one imagined movement type that could be classified significantly from rest in the complex condition (M = 62.74%, SD = 3.73%). These findings suggest that using more complex imagined movements with an EEG-based BCI for patients will allow for successful motor signal classification among more individuals. Future investigations will examine the role of experience with particular actions and apply other analysis techniques to improve classification accuracy.

2-F-173 Optogenetic probing of GABAergic modulation of sleep-wake states

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The sleep-wake cycle is a highly-conserved physiological process across all vertebrates. Sleep-wake switches result from a complex, yet undefined, inhibitory/excitatory balance between cells and neural circuits distributed throughout the brain. Here, we focused our investigation on the role of inhibitory cells in the lateral hypothalamus (LH) on sleep-wake states since the LH contains both sleep and wake circuits. To precisely control the activity of LH GABA cells, we bilaterally infused AAV-Ef1a-DIO-ChETA-eYFP virus into the LH of VGAT::Cre mice. FISH/immunohistochemical labeling confirmed high selectivity (> 95%) of the targeting approach. Electrophysiological recordings in acute brain slices from transduced animals demonstrated that brief blue light pulses (1-5 ms) reliably evoked single action potentials up to 50 Hz. In vivo, we found that semi-chronic bilateral optical activation of LH GABA cells at 20 Hz, but not 1 Hz, increased by 2-fold wake duration. These results were confirmed using real time detection of EEG/EMG to drive optical stimulation selectively during either NREM or REM sleep. Further, we identified both anatomically and functionally a direct connection between LH GABA neurons and neurons located in the reticular thalamic nucleus (RTN), a nucleus involved in sleep spindle generation. Interestingly, activation of the LH GABA terminals in the RTN at 20 Hz was sufficient to induce sleep-to-wake transitions. Collectively, these data suggest that GABA projections from the LH to the RTN represents a direct arousal circuit to thalamic and cortical structures.

2-F-174 Adult neurogenesis protects against proactive interference

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Neurogenesis occurs throughout life in the mammalian hippocampus. As a result, the hippocampal circuitry is in a constant state of flux. This plasticity has potential implications for the clearance of outdated memories. The fidelity of a hippocampus-dependent memory may be decreased by adding new neurons. Therefore, we sought to determine whether increasing neurogenesis after learning would decrease the stability of that memory and if so, whether that would lead to an improvement in reversal learning. Mice were trained in one of three hippocampus dependent tasks, a spatial version of the Morris

water task, a touchscreen based object-location paired associates task and a digging mediated odour-context paired associates task. Following training neurogenesis was increased with either voluntary wheel running or administration of the NMDAR antagonist, memantine over a period of 4 weeks. We then measured retention of the previously acquired memories and conducted reversal learning. In all three tasks our results show that a post-training increase of neurogenesis causes a decrease in retention of previously acquired hippocampus-dependent memories. However, when subjected to reversal learning, mice with elevated levels of neurogenesis outperformed mice with normal levels of neurogenesis. The results described here show that adult neurogenesis aids in the clearance or inhibition of outdated memories. As a result new learning can occur more efficiently due to decreased proactive interference from the previous memories.

2-F-175 Post-trial treatment with the D1-like receptor antagonist SCH 23390: disruption of memory consolidation or emergence of state-dependent memory?

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Post-training administration of drugs that block dopamine (DA) D1-like receptors has been shown to affect memory consolidation in a number of conditioning paradigms. DA D2-receptor preferring antagonist haloperidol (0.25 mg/kg, i.p.), repeatedly injected in a particular environment, produces day-to-day increases in catalepsy, quantified by time spent on a horizontal bar without active movement. Places associated with repeated haloperidol injections and catalepsy tests also elicit catalepsy, now conditioned. We examined the effects of post-trial treatment with the D1-like receptor antagonist SCH 23390 (0.05 mg/kg, i.p.) on development of catalepsy sensitization and acquisition of conditioned catalepsy. Haloperidol did not elicit cataleptic responses in the initial session; however, rats developed sensitization with repeated testing. When rats were injected and tested with saline, the 0- and 15-min (but not 60-min) post-trial SCH 23390 groups failed to exhibit significant conditioned catalepsy, suggesting that D1-like receptor antagonism disrupted consolidation of drug-environment pairing in a time-dependent manner. However, when all animals were subsequently challenged with SCH 23390, the 0-min (but not 15- or 60-min) group exhibited a significant catalepsy response, suggesting that immediate post-trial SCH 23390 treatments produced a drug stimulus insertion effect that contributed to the acquisition of a state-dependent memory. Our findings demonstrate that a drug stimulus can become a conditioned stimulus when given post-trial during the consolidation period.

2-F-176 The Role of Cholinergic Signaling in the Pedunculopontine Tegmental Nucleus

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Cholinergic signaling plays a role in many neurodegenerative disorders. While disruptions in dopaminergic signaling are known to be involved in Parkinson's disease (PD) and progressive supranuclear palsy (PSP), it is now recognized that cholinergic dysfunction may also play a role in behavioural abnormalities. Post-mortem studies of individuals with PSP reveal that the pedunculopontine tegmental nucleus (PPT), an area rich in cholinergic neurons, is degenerated, showing 60% neuronal loss. However, the contribution of cholinergic PPT activity for behavioral abnormalities is poorly understood. Here we investigate the contributions of PPT acetylcholine (ACh) release on cognitive behaviours by the selective elimination of the vesicular ACh transporter (VAChT), a protein responsible for synaptic storage and release of ACh, in murine PPT cholinergic neurons. Brainstem VAChT knockout mice were generated using a Cre/LoxP system under the control of the En1 promoter. Analysis of several behavioural parameters indicates that elimination of VAChT has several consequences in PPT-related tasks. Mutant

mice presented normal anxiety-like behaviour, however these PPT VAChT mutant mice presented anti-depressant behaviour. These mice also presented gait abnormalities. In contrast with recently reported PPT choline acetyltransferase knockout mice using the same En1 Cre mice, our mutants were not hypokinetic. Our experiments will contribute to understanding the role of PPT cholinergic neurons for behavioural functions in diseases that affect dopamine-ACh balance, such as PD and PSP.

2-F-177 Effect of GSK3-Beta Inhibition on the Acquisition and Expression of Intra-Accumbens Amphetamine-Induced Conditioned Place Preference in Rats

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The conditioned place preference (CPP) paradigm measures the rewarding effects of substances. Rats administered a dopamine (DA) agonist such as amphetamine (AMPH) in one chamber, but vehicle in another, show a preference for the drug-paired chamber when they have free access to both. GSK3¦Â, a molecule downstream of DA D2 receptors, is implicated in conditions of DA dysfunction such as addiction and schizophrenia. We tested the hypothesis that the GSK3¦Â inhibitor, SB 216763 (SB), will differentially affect the acquisition and expression of AMPH-induced CPP. The CPP protocol consisted of 3 phases: 3 days of habituation (free access to both sides: 15 min), 8 days of conditioning (alternating vehicle and drug days restricted to one side: 30 min), and 1 day of testing (free access to both sides: 15 min). In the acquisition paradigm, rats were administered either SB (0.5, 3.0 ¦Ìg/0.5 ¦Ìl/side) and AMPH (20 ¦Ìg/0.5 ¦Ìl/side) or DMSO (SB vehicle, 0.5 ¨¬l/side) and saline (AMPH vehicle, 0.5 ¦Ìl/side) prior to conditioning, and no drugs on the test day. In the expression paradigm, rats were administered either AMPH (20 ¦Ìg/0.5 ¦Ìl/side) or saline (0.5 ¦Ìl/side) during conditioning, and SB (0.5, 3.0 ¦Ìg/0.5 ¦Ìl/side) prior to testing. All drugs and vehicle were administered via intra-cranial microinfusions into the nucleus accumbens. At a dose of 3.0 ¨¬g/0.5l/side, SB blocked the acquisition and expression of AMPH-induced CPP. Results implicate GSK3¦Â signaling in the acquisition and expression of AMPH-induced CPP, implicating GSK3¦Â in the rewarding properties of AMPH. (Funded by NSERC).

2-F-178 Familiarity-based recognition response patterns for faces, buildings, and chairs in perirhinal and parahippocampal cortex

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An unresolved question in our understanding of the medial temporal lobes is how functional differences between structures pertaining to stimulus category relate to the distinction between item- and contextually-based recognition-memory processes. Specifically, it remains unclear whether perirhinal cortex (PrC) supports item-based familiarity signals for all stimulus categories or whether parahippocampal cortex (PhC) may also play a role for stimulus categories that are known to engage this structure in other task contexts. We employed multi-voxel pattern analyses of fMRI data to compare patterns of activity that are associated with the perceived familiarity of faces, buildings, and chairs. During scanning, participants judged the familiarity of previously studied and novel items from all three categories. In right PrC, we found patterns of activity that distinguished subjectively familiar from novel faces. In right PhC, by contrast, we observed such patterns for buildings. Familiarity signals for chairs were present in both structures, but shared little overlap with the patterns observed for faces and buildings. In the hippocampus, we found no evidence for familiarity signals for any object category. Our findings show that both PrC and PhC contribute to the assessment of item familiarity, with evidence for category specificity in their response profiles. They suggest that PhC does not only represent context, but can also represent item information for some object categories. Our findings also indicate that involvement of PrC in representing familiarity is not ubiquitous.

2-F-179 Statistical regularities in multiple memories are extracted over time

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Studies suggest that over time memories are generalized. This is consistent with a computational hypothesis which posits that during rest the neocortex continues to learn about statistical regularities in previously formed memories. However, whether memories are transformed via a time-dependent detection of statistical patterns has not been previously tested. Here, we use a modified version of the Morris water-maze to determine whether the passage of time increases an animal's awareness of regularities in spatial memories. For 9 days, mice were trained to find a submerged platform that appeared in a different location on each day. The locations were drawn from a normal distribution in polar co-ordinates, which induced a statistical pattern. When probed with no platform, a 30 day delay before the probe (vs. 1 day) produced search paths that were significantly more similar to the platform distribution, as measured by the Kullback-Leibler divergence. This suggested that the animals' memories had been compressed to match the distribution. To explore this further, we examined the effects of placing the ninth platform at the mean of the distribution (High P) vs. a region with zero probability (Low P). Based on the escape latencies, we found that a 30 day delay between the last two days of training made it significantly more difficult for the mice to learn the Low P platform, i.e. the location which didn't match the pattern contained in their old memories. Our data supports the hypothesis that the brain extracts statistical regularities contained in multiple memories over time.

2-F-180 Resting-state cross-frequency coupling predicts reaction times in a verbal recognition task.

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When not engaged in a cognitive or behavioral task, the brain displays resting-state activity characterized by patterns of non-random oscillations. These oscillations cover a broad range of frequencies that interact such that the phase of a lower frequency regulates the amplitude of a higher frequency, thus promoting coherent communication within and between distinct cortical regions oscillating at different rhythms. It is unclear, however, to what extent this interaction across frequencies, termed cross-frequency coupling (CFC), influences cognitive processes. Here, we examine this question by monitoring resting-state EEG activity in participants promptly prior to their performing a verbal recognition task. We found that faster reaction times in this task were associated with more prominent CFC during resting-state activity in localized cortical areas. These results integrate two areas of investigation. A first area states that CFC promotes memory and attention by merging functional networks across spatiotemporal scales, while a second area indicates that cognitive performance incorporates a number of the same networks that are also employed during resting-state activity. We provide a bridge between these findings by showing that resting-state CFC relates to cognitive performance, and by clarifying the frequency and topographical localization of this effect

2-F-181 "Erasing" a cocaine-cue memory

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Exposure to stimuli that were associated with prior drug use can awaken powerful memories that may trigger drug craving and relapse. Understanding how animals learn and remember the association between a cue and a drug of abuse is a crucial step to develop more effective treatment strategies for addiction. CREB (cAMP/Ca2+ responsive element

binding protein) is a transcription factor that has a well-documented role in neuronal plasticity and long-term memory formation. Previously we found that increasing levels of CREB in a subset of lateral amygdala (LA) neurons enhanced the formation of a fear memory and that selectively ablating these neurons essentially "erased" the fear memory. We took advantage of this approach to investigate if LA neurons are also critically involved in a cocaine-cue associated memory. To assess cocaine-cue memory, we used the conditioned place preference (CPP) paradigm. We microinjected HSV vectors encoding CREB or GFP in a small proportion (~15%) of LA neurons. Increasing CREB in LA during (but not after) conditioning enhanced cocaine-CPP memory. To determine if these LA neurons with increased CREB function comprised a crucial component of the cocaine memory-trace, we used inducible diphtheria toxin receptor (iDTR) transgenic mice to selectively ablate these neurons. Post-conditioning deletion of LA neurons with increased CREB function (but not random neurons) blocked subsequent cocaine-CPP memory. Our results indicate, similar to a conditioned fear memory, a small population of LA neurons is critically involved in a cocaine-associated memory.

2-F-182 Role of Pannexin 1 in Olfaction and Memory

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Pannexins are a class of channel proteins sharing structural homology to innexins, able to form large pores conducting molecules like ATP upon activation. Since their discovery, a lot of effort has been made to understand their contribution to ATP release in various tissues, as purinergic signaling is involved in a huge variety of physiological processes. In the olfactory epithelium (OE), ATP modulates olfactory responsiveness, and plays a role in proliferation and differentiation, a process continuously taking place in the OE, as neurons are replaced throughout the whole lifespan. ATP was further shown to be released in the vomeronasal organ (VNO), an organ involved in pheromone detection, and to modulate sensory neuron function. In this study, we show that Pannexin 1 (Panx1) is expressed in the OE and VNO. A Panx1 KO mouse line was used to investigate impairments on olfactory and vomeronasal function. No significant impairment in the olfactory system was found, but minor changes in social behavior were detected. We conclude that Panx1 is involved in memory formation, but dispensable for olfaction.

2-F-183 Lifelong Bilingualism Is Associated with Larger Grey and White matter Volumes in the Temporal Lobe

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The goal of this study was to identify volumetric differences between lifelong bilinguals and monolinguals. A number of studies have provided evidence for functional neural plasticity associated with language experience; but few have extended to volumetric comparison in brain structures. Because prolonged bilingual experience is associated with brain reserve, we predicted volumetric differences in regions relevant to language processing. Monolingual (n=14) and bilingual (n=14) older adults were matched in age (M = 70), gender, years of education, English proficiency and neuropsychological task performance. Bilingual older adults reported active usage of two languages before the age of 11. Whole brain T1-weighted images were collected and estimates of lobar grey matter (GM) and white matter (WM) were estimated using an adapted version of the ANIMAL algorithm (Collins, 1995). Freesurfer software provided segmentation of subcortical structures, including the hippocampus (Fischl, 2002 and 2004). Volumetric comparisons

were made between groups, examining the frontal, temporal, parietal, and occipital lobes separately. Excluding one outlier bilingual participant with lower hippocampal volume, significantly greater volumes in bilinguals were observed: left and right temporal WM (L: p=0.016, R: p=0.002); total (GM and WM) left and right temporal lobes (L: p=0.038, R: p=0.038). Results suggest bilingual experience is associated with higher GM and WM volumes in the temporal lobe. Prolonged bilingual experience may be a cognitive reserve factor that is associated with brain reserve.

2-F-184 Anxiolytic effect of a VAChT-overexpressing BAC transgene in B6eGFPChAT mice

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Cholinergic neurotransmission, particularly from the basal forebrain to the cortex and hippocampus, has been long associated with anxiolytic behavioral effects. The specific contribution of the vesicular acetylcholine transporter (VAChT) on anxiety-like behavior is less understood. Here, we used B6eGFPChAT transgenic mice that contain four copies of the RP23-268L19-EGFP transgene. RP23-268L19-EGFP contains the VAChT and choline acetyltransferase (ChAT) promoter and coding regions, in which ChAT transcription is terminated and replaced by enhanced green fluorescent protein. As such, B6eGFPChAT mice overexpress VAChT in cholinergic neurons while levels of other cholinergic components (i.e. ChAT) are maintained. We hypothesized that increased VAChT expression observed in B6eGFPChAT mice may contribute to reduced anxiety. To test this hypothesis, we used the elevated plus maze, open-field and light-dark aversion task. In the elevated plus maze, B6eGFPChAT mice spend more time in the open arm than B6 controls, which was matched with reduced time spent in the closed arm. B6eGFPChAT mice also accumulated greater total distance during the elevated plus maze task compared to B6 controls. While the open field and dark/light aversion paradigms did not reveal genotype effects in their primary outcome measures, each test reiterates the release of exploratory inhibition in B6eGFPChAT mice through increased locomotor activity. Taken together, these results suggest that the VAChT-overexpressing BAC transgene in B6eGFPChAT may be sufficient to decrease measures of anxiety-like behaviour.

2-F-185 Investigating the temporally-graded retrograde amnesia using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs)

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Animal studies in neuroscience often involve lesions or pharmacological interventions that suffer from the lack of cell-type specificity, and imprecise control over timing and the extent of damage. Recent development of reversible, non-invasive pharmacogenetic tools has helped overcome these insufficiencies, giving scientists much finer temporal and spatial controls. Here, we use a designer receptor (hM4Di) to investigate the temporal gradient of memory consolidation, and examine the much debated role of hippocampus in this process. To silence excitatory hippocampal neurons at dorsal CA1, mice were first infused with adeno-associated virus containing hM4Di under the CaMKII promoter. The specificity of neuronal silencing in hM4Di cells with the designer drug clozapine-N-oxide (CNO) was confirmed in vitro via patch-clamp recordings, and in vivo via analysis of the immediate early gene c-Fos expression. Following surgery, mice were trained in a standard contextual fear conditioning paradigm, and injected with CNO or vehicle prior to testing either 1 day (recent) or 28 days (remote) later. Mice that received CNO showed significantly less freezing than controls in the recent, but not remote, memory test. The data is consistent with previous lesion work, suggesting that the hippocampus is necessary for the expression of recent fear memory, while other brain regions may be sufficient to support remote memory. This work

also demonstrates DREADDs as a reliable tool with high temporal and spatial fidelity, and is ideal for exploring the temporal gradient of memory reorganization.

2-F-186 The Separate and Combined Effects of Monoamine Oxidase Inhibition and Nicotine on P50 Sensory Gating

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While it has long been observed that schizophrenia patients have an increased rate of smoking compared to both the general public and other psychiatric populations, the precise link between smoking and schizophrenia is still unclear. It has been suggested that patients with schizophrenia may be using nicotine to self-medicate against cognitive deficits associated with lower expressions of the alpha-7 subunit of the nicotinic receptor (nAChR). Because chronic smoking has been shown to decrease monoamine oxidase levels in both patients and the normal population, this study sought to examine the separate and combined effects of acute nicotine and pharmacologicaly inhibited monoamine oxidase on auditory P50-measured sensory gating in a group of 24 non-smoking healthy males. The paired-click paradigm was used to measure sensory gating under placebo, nicotine gum, moclobemide, and a combination of nicotine and moclobemide. Efficient gating individuals were divided from poor gating individuals via median split based on gating scores at baseline. It was found that the combination of nicotine and moclobemide improved gating in poor gating individuals and maintained gating in efficient gating individuals. It is possible that the poor gating individuals in this study could serve as a model for the gating deficiency observed in schizophrenia patients, and the improvement of which through monoamine oxidase inhibition and nicotine may indicate an improvement in dopaminergic signal-to-noise ratio thought to be impaired in schizophrenia.

2-F-187 Preserved IEG reactivation in the hippocampus and prefrontal cortex across days

***Ali Gheidi*[1], Elham Satvat[2], Irina Odintsova[1], Diano Marrone[1]**
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Formation of long-lasting memory is imperative to the survival of all species. In the mammalian brain, stable memory functioning is thought to critically depend on a reactivation of the original experience; this might be accomplished by a memory trace. Moreover, from a systems perspective new memories may be hippocampal dependent while as a memory stabilizes it may be cortex dependent. To address this issue, we used compartment analysis of temporal activity by fluorescence in situ hybridization (Arc catFISH) to track changes in CA1 and Infralimbic, Prelimbic and Cingulate of the prefrontal cortex across days. Rats were given a single assisted ambulatory experience and were either sacrificed immediately or with 25 min delay. Results show that by day 36, reactivation is seen in the hippocampus and prefrontal cortex of rats sacrificed after a delay (with the exception of Infralimbic). In conclusion, reactivation may be a robust phenomenon that remains active with repetitive training.

2-F-188 Effects of CCK-4 on the Unconditioned Acoustic Startle Response in Mice

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Cholecystokinin (CCK) induces panic attacks in humans and increases fear behavior in rats by way of CCK-B receptors. First, we will investigate the effects of CCK-4 and CCK receptor blockers on the unconditioned acoustic startle response in C57BL/6 mice. Second, we will visualize different neural populations in the amygdala that co-localize with CCK neurons and CCK terminals. Thus far, our behavioural results suggest that an i.p. dose of

10mg/kg of CCK4 potentiates startle, while lower doses (0.1mg/kg-3mg/kg) have the opposite effect. CCK-B receptor blockers L-365,260, PD135158 and LY288513 inhibit the effects of CCK-potentiated startle.

2-F-189 Just once: How can a single experience with sucrose instigate craving and addiction?

Justin McGee Odger[1], **Roelof Eikelboom**[1]
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Grimm et al (2004) found craving for sugar (and cocaine) can increase over a lengthening period of abstinence before eventually declining. A single exposure to morphine can elicit symptoms of withdrawal (Schulteis et al 2005), suggesting that neurological changes occur almost immediately. We examined the changes in 24 h sucrose solution (4%) consumption after various periods of abstinence when rats had received only one day's exposure. First rats were given 24 h sucrose access, followed by 0, 2, 8, or 26 days without access (4 groups of 8). Groups were given eight days access to sucrose following the abstinence. After the 8 days of sucrose access another abstinence period was implemented, 8, 2, 8, or 26 days for each group respectively. The animals were assigned to groups so that the initial day's sucrose consumption did not differ (~150g). All rats given sucrose solution after a period of abstinence consumed more (~230g) than rats with no abstinence period who remained at about 150g. Over the course of 8 days these differences between groups disappeared with sucrose consumption declining to ~170g. All groups showed an increased consumption after the second abstinence period and then gradually reduced their intake to baseline levels. These results suggest that a single 24 h experience with a weak sucrose solution can produce an abstinence induced increase in consumption that was remarkably robust over the course of a month.

2-F-190 Spatial and contextual cues are necessary for the hippocampus to mediate estrogenic effects on social recognition but not object recognition

Anna Phan[1], **Sarah Suschkov**[1], **Nir Pecchioli**[1], **Lisbette Seguin**[1], **Boyer Winters**[1], **Neil MacLusky**[1], **Elena Choleris**[1]
[1]University of Guelph

Recently, we showed low doses of systemic 17β-estradiol improved object placement, object recognition and social recognition learning in ovariectomized mice within 40min of treatment (Phan et al., 2012. Neuropsychopharm, 37:2299), which appears to be mediated through ERα rather than ERβ (Phan et al., 2011. Endocrinology, 152:1492). 17β-estradiol and an ERα agonist also increased CA1 hippocampal dendritic spine density, whereas an ERβ agonist had no effect or decreased spine density. Furthermore, current experiments from our lab demonstrate that intrahippocampal delivery of 17β-estradiol improved performance on object placement, object recognition and social recognition learning paradigms. While the involvement of the hippocampus in object placement is well established, its role in social and object recognition is less clear. Some evidence suggests the hippocampus becomes involved in these tasks only when spatial and contextual information is available. Thus we repeated the above intrahippocampal 17β-estradiol experiments in a Y-apparatus, which minimizes the spatial and contextual information available to mice. We found intrahippocampal 17β-estradiol improved object recognition, but it no longer facilitated social recognition. Therefore, estradiol in the hippocampus appears to directly improve object recognition and placement learning, but it indirectly facilitates social recognition only when spatial and contextual information is available. Hence, other brain areas are likely to directly facilitate the rapid effects of estradiol on social recognition. Funded by NSERC.

G – Novel Methods and Technology Development

2-G-191 Bacterial Expression of Biologically Active ProNGF

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Nerve growth factor (NGF) is a neurotrophin that promotes neuronal survival and maintenance. The study of proNGF, the predominant form of NGF in the brain, is critical for understanding neurodegenerative diseases. For this research to be possible, large quantities of proNGF must be easily and affordably obtainable. However, when expressed in bacteria, proNGF forms non-functional aggregates that deposit into inclusion bodies. Our aim is to express recombinant proNGF in a bacterial system in a soluble and biologically active form. Four proNGF cDNA constructs were generated using Gateway Cloning Technology and were expressed in E. coli Origami B pLysS cells. Each construct produced soluble proNGF. ProNGF with a C-terminal histidine (His6) tag was purified using nickel affinity chromatography. The purified proNGF was tested for activity in a MAPK activation assay. MAPK phosphorylation was observed following addition of purified proNGF-His6 to PC12 cells, suggesting that purified proNGF-His6 is biologically active. Cell survival and neurite outgrowth assays will be done to further confirm that the recombinant proNGF is biologically active.

2-G-192 A simple method for non-destructive 3D immunostaining of the mouse brain

Jacqueline Gleave[1], **R. Mark Henkelman**[1], **Jason Lerch**[1], **Brian Nieman**[1]
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A goal of many studies is to understand the changes in cell distribution that occur as part of disease progression. Typically this is done using sectioning and immunostaining. However, many structures or cell distributions are not readily appreciated in two-dimensions (2D) and would benefit from three-dimensional (3D) representation. 3D optical imaging has the ability to visualize cells of interest using transgenic optical markers (fluorescent proteins). A more flexible approach would make use of antibodies used for traditional 2D immunostaining to visualize cells of interest. However, 3D immunostaining in the mouse brain has been largely hampered by penetration problems. We have developed a staining method that allows for large mouse brain samples to be immunostained. This method is simple and easy to apply using a combination of heat, time, and a modified fixation protocol. It does not require the use of specialized equipment making it accessible to any laboratory. We have rigorously evaluated the quality of the staining in mouse brain samples and show the potential of this method to visualize cell distribution in 3D using optical projection tomography (OPT) and serial two-photon tomography. Figure 1. OPT was used to image a 3D immunostain of doublecortin (DCX), which marks migrating neuroblasts. a)Optical slices show the expected staining pattern for DCX. b)The 3D distribution of the DCX cells along the lateral ventricles shows the DCX migratory chains. c)A maximum intensity projection shows the cells migration pattern from the lateral ventricles to the olfactory bulbs.

2-G-193 Visualization and Phospholipid Identification: a tool for the aid in identification of lipids via mass spectrometry

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Advances in lipid mass spectrometry (MS) have allowed for the identification of specific lipid species, as opposed to general lipid classes. Where genomics and proteomics capitalize on sequence-based signatures, glycerophospholipids lack easily definable molecular fingerprints. This makes identification from mass spectrometry spectra a highly labour-intensive process. Given increasing MS sensitivity, many m/z values are not represented in existing prediction engines. In order to address this gap, we created Visualization and Phospholipid Identification (VaLID), a freely accessible web-based application that returns all of

the theoretically possible phospholipids for a given m/z value and MS condition. The application contains molecular species of eight glycerophospholipid classes, with fatty chains ranging from 0 to 30 carbons in length, with up to 6 unsaturations, and attached to the glycerol backbone through an ester, ether, or vinyl-ether linkage. An updated version of VaLID for presentation to the Canadian Association of Neuroscience includes a ninth glycerophospholipid class. The application can also draw structural diagrams of all permutations for each lipid within the database, and curated lipids detected by the Canadian Institute of Health Research Training Program in Neurodegenerative Lipidomics (CTPNL) are provided as high-resolution three dimensional images. VaLID is available through the CTPNL website at https://www.med.uottawa.ca/lipidomics/resources.html.

2-G-194 3D Culture for In Vitro Modeling of Glial Scarring

Andrea Jeffery[1], **Matthew Churchward**[1], **Anastasia Elias**[1], **Kathryn Todd**[1]
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Neural interfacing often requires electrode implantation into the central nervous system (CNS). These electrodes must be biocompatible (elicit a minimal foreign body response) to optimize long-term safety and functionality. Due to variability, expense and time required for in vivo testing, a parallel in vitro model is desired. This study investigates the use of a three-dimensional culture technique to analyze microwire glial scarring. Two-dimensional in vitro testing has been used previously to quantify and monitor the progression of glial scarring over 14 days at the electrode (proliferation of nearby immune cells and electrode encapsulation). Results demonstrated a quantifiable and representative model of glial scarring. To compensate for electrode shifting and limited modeling of mechanical properties in 2D, a hyaluronan (HA) based three-dimensional cell culture model was developed. Viability of microglia and astrocytes within the gel at various seeding densities was monitored over 7 days. At a seeding density of 10^8 cells/mL, both viability and cell attachment improved. The gel did not interfere with cell characterization and greatly reduced electrode shifting during culture and immunolabeling. Dynamic mechanical analysis was used to measure changes in gel stiffness with varying HA oligomer concentration, allowing the gel to mimic the mechanical properties of neural tissues. A new 3D HA hydrogel culture model will allow in vitro testing of the physical and chemical properties of neural interfacing electrodes in in vivo-like conditions.

2-G-195 Rock-a-bye baby: using slice-by-slice motion estimation and correction to improve the sensitivity of neonatal fMRI

Conor Wild[1], **Rhodri Cusack**[1]
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The effect of brain injury on a newborn is difficult to assess, as the behavioral manifestations of disrupted function are initially subtle. Functional magnetic resonance imaging (fMRI) may provide an invaluable tool for more directly studying brain function in this population. However, fMRI takes many tens of minutes to acquire and head motion is a significant issue because these subjects cannot be instructed to remain still. Traditional rigid-body fMRI motion correction performs poorly for data sets with large motion artifacts, partly because it makes the implausible assumption that the head is stationary during each volume acquisition. As a result, slices within a volume can be out of alignment with each other, and equivalent voxels in adjacent volumes might sample different brain regions. Here, we implement a slice-by-slice motion estimation and correction algorithm to improve the sensitivity of neonatal fMRI. Our method aligns each slice in the fMRI time series to a template image while constraining the motion trajectory to a realistic model of subject motion. So far, the algorithm has been evaluated on fMRI data collected from 7 neonates in a somatosensory stimulation paradigm. Compared to rigid-body

realignment, our slice-by-slice method increased the peak t-statistic of activation in somatosensory cortex in 6/7 subjects. Furthermore, our method revealed activation in one subject for whom no activation was observed with standard pre-processing. Continuing work includes testing more neonatal data sets, and optimizing the algorithm to use parallel hardware.

2-G-196 ConJUNGtion: a tool for brain connectivity analysis and auditory stimulus design

Gleb Bezgin[1], **Anthony McIntosh**[1]
[1]Rotman Research Institute

Recent progress in neurosciences urged the need to develop software tools for data analysis and visualization. A broad field in modern neuroscience, known as "connectomics", is one of the most prominent instances providing this request. The abundance of different neuroimaging modalities involve complex data mining procedures, and the notion of "connectivity" derived from each of these modalities may refer to entities very different in anatomical, physiological and technical senses. Here we describe a tool for analysis of brain networks derived from various modalities. It implements direct queries to an extensive axonal tract tracing database, currently constituting the gold standard of structural connectivity. Options for browsing brain regions in the database, and querying them by specifying coordinates from widely used brain spaces are provided. Resulting graphs can be assembled and analyzed with some common (e.g., degree) and more recently introduced (e.g., Markov Centrality) metrics. They can also be visualized on brain templates and quantitatively compared to graphs obtained from other modalities. The tool also allows users to design auditory stimuli. Users can create and edit midi files by querying a local sound database or directly specifying note sequences. Several metrics evaluating perceptual characteristics (i.e. dissonant vs. consonant, sad vs. happy, one musical scale vs. another) of resulting musical sequences are provided. Overall, the tool offers a flexible utility for graph-theoretical analyses, and novel sound stimulus development features.

2-G-197 Laser Speckle Contrast Imaging during Blood Brain Barrier opening

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The blood brain barrier (BBB), which regulates the exchange of substances between the blood and the brain parenchyma, is believed to play a role in the development of many brain disorders. Until now, the main method used to study its integrity was fluorescence imaging. We hypothesized that a compromise in the BBB integrity would have an effect in brain hemodynamics and that this effect would be different for arteries and veins. This hypothesis was consolidated by our micro-fluidic simulations. As Laser Speckle Contrast Imaging (LSCI) is a powerful tool to obtain flow velocity maps intrinsically (without a fluorescent agent), we evaluated the performance of LSCI in monitoring BBB disruptions. Our results show that BBB opening was associated with a discrepancy of the relative arteriole and venule LSCI cross-sectional flow profiles. The balance between venous and arterial flow dropped significantly in rats treated with compounds known to compromise the BBB integrity (0.78 ± 0.06 for lipopolysaccharide and 0.70 ± 0.07 for deoxycholic acid) compared with controls (1.03 ± 0.04). These results demonstrate that LCSI can be used as an innovative, low-cost, and label-free method to monitor blood brain barrier integrity in a live rodent brain. This work was supported by the Natural Sciences and Engineering Research Council of Canada and the Canadian Institutes of Health Research.

2-G-198 Ultra-Bright and -Stable Red and Near-Infrared Squaraine Fluorophores for In Vivo Two-Photon Imaging

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Fluorescent dyes that are bright, stable, small, and biocompatible are needed for high-sensitivity two-photon imaging, but the combination of these traits has been elusive. We identified a class of squaraine derivatives with large two-photon action cross-sections (up to 10,000 GM) at near-infrared wavelengths critical for in vivo imaging. We demonstrate the biocompatibility and stability of a red-emitting squaraine-rotaxane (SeTau-647) by imaging dye-filled neurons in vivo over 5 days, and utility for sensitive subcellular imaging by synthesizing a specific peptide-conjugate label for the synaptic protein PSD-95.

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

2-H-199 Brain Imaging And Decisions About Life-Sustaining Treatment

Adam Shriver[1]
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In recent years, researchers have used brain imaging techniques to demonstrate awareness in subjects previously diagnosed as being in persistent vegetative states (Monti et al. 2010, NEJM; Owen et al. 2006, PNAS). In response to this research, some bioethicists have argued that, "the discovery of consciousness in very severely brain-damaged patients may give us more reason to discontinue life-sustaining treatment than to continue it," (Wilkinson et al. 2009 J Med Ethics). Among the reasons provided for this conclusion are the claims that patients might be in a state of extreme suffering with no ability to communicate and that patients could have no hope of enjoying the positive features of the world : I argue that breakthroughs in the past three years significantly undermine the relevance of both of these claims in regards to the question of whether additional imaging assessment should be made prior to decisions to withhold life-sustaining treatment. The ability to use imaging to detect responses to yes or no questions (Monti et al. 2010, NEJM) challenges the assumption that we would need to guess about whether patients in these states "may" be suffering after detecting awareness through imaging. In response to the claim that the patients have no hope of enjoyment of future positive features of the world, recent progress in brain-machine interface (Naci et al. 2010; Annals of Neurology) suggests that using neurofeedback to communicate with the world is a tractable, if still difficult, problem. Thus, patients with awareness have hope for future communication

2-H-200 First Intoxication with Alcohol in Early Adolescence is Associated with Higher Lifetime and Ongoing Use of Many Psychoactive Drugs in University Students

Mary Beth Dunn[1], **Bruce McKay**[1]
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The younger an individual is when they first become intoxicated with alcohol, the more likely they are to use, abuse, and become dependent on alcohol later in life. However, most research conducted on age of first alcohol intoxication in relation to later substance use and harmful outcomes has focused on people from low income neighborhoods, and/or who are lifetime drinkers, and/or who were classified as 'at risk' children, and/or who came from families negatively affected by substance abuse, and/or people who currently exhibit psychiatric disorders as well as very serious (typically heroin or crack cocaine) substance use disorders - characteristics not typically found in university students. Many drug education programs, which are implemented on the population at large, are developed based on the results gathered from these high risk populations. It is important to determine then if a similar increase in substance use, abuse, and/or dependency later in life is associated with age of first intoxication when considering university students. Here we have studied how age of first intoxication with alcohol relates to current and lifetime use of alcohol and other psychoactive drugs, current drug

abuse and dependency, and academic and legal outcomes, in a large sample of undergraduate university students. We have further examined the risk and protective factors that are related to their age of first intoxication with alcohol. Neural mechanisms relevant to the early use of intoxicants that may contribute to the observed outcomes will also be discussed.

2-H-201 Factors associated with methadone dose in men and women undergoing Methadone Maintenance Treatment (MMT)

***Monica Bawor*[1], Brittany Dennis[1], Carolyn Plater[2], Guillaume Pare[1], Andrew Worster[3], Michael Varenbut[2], Jeffrey Daiter[2], David Marsh[4], Dipika Desai[1], Lehana Thabane[1], Zainab Samaan[1]**
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BACKGROUND The effectiveness of MMT depends on appropriate methadone dose. Biological and environmental factors are important in determining methadone dose because they influence the pharmacodynamics of medications, thus drug safety and efficacy. HYPOTHESIS Methadone dose is positively correlated with biological factors including age and BMI, and environmental factors including smoking and MMT duration. The effect of these factors is sex specific. METHODS Subjects (n=251) from the Genetics of Opioid Addiction Study undergoing MMT were assessed. Demographic details, methadone dose, and anthropometric measures were obtained. Statistical analyses were performed using SPSS 20 software. RESULTS Overall, men are older, smoke more cigarettes/day, and remain on methadone longer than women. For men and women, there is a significant association between methadone dose and number of cigarettes smoked/day (OR: 1.19, p=0.001) and methadone duration (OR: 0.38, p<0.001). Age is associated with methadone dose in women (OR: 1.19, p=0.042), but not men. Number of cigarettes smoked/day is associated with methadone dose in men (OR: 1.43, p=0.006), but not women. No correlation was found between methadone dose and age of initial opioid use, number of years smoking, or BMI. CONCLUSION Preliminary results suggest that the association between methadone dose and age, smoking status, and MMT duration varies in men and women, indicating that the impact of these variables on methadone is sex-specific. Small sample size and confounders such as substance use and comorbidities may explain these findings.

Poster Session 3

A - Development

3-A-1 Altered brain development in an early-onset mouse model of Alzheimers disease

Rylan Allemang-Grand[1], **Jan Scholz**[1], **Jacob Ellegood**[1], **Christine Laliberte**[1], **Paul Fraser**[1], **John Sled**[2], **Jason Lerch**[1]
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Mouse models of Alzheimer's disease (AD) are used to draw associations between brain atrophy and underlying neuropathology. Cross-sectional analyses demonstrate atrophy in similar regions of the brain implicated in human AD, suggesting that these models recapitulate disease progression. However, these studies limit their analyses to a few time points after the onset of plaque deposition. Therefore, we set out to longitudinally track the anatomical changes before and after plaque deposition in the TgCRND8 mouse model of AD. We hypothesized that volumetric atrophy will closely parallel the time course of AD-related pathological features. Transgenic and wild-type litter mates were longitudinally scanned with a manganese-enhanced MRI (MEMRI) protocol before (4 & 9 weeks) and after (12, 16, 20 & 24 weeks) the onset of plaque deposition. Additionally, we scanned a separate cohort of 1-week-old transgenic and wild-type mice with 3D diffusion-weighted imaging. Acquired images were registered, deformed to generate a consensus average and volumes were computed for 62 brain regions. At 4, 9 and 12 weeks, transgenic mice had an 8% reduction in the volume of the cortex, hippocampus, olfactory bulbs and cerebellum. Localized expansion of the amygdala was also apparent at this time. Analysis of the 3D diffusion weighted images demonstrate that that many of the anatomical differences at the later time points were apparent at 1 week of age, 11 weeks before the onset of plaque deposition. These findings suggest that the anatomical differences may be associated with a developmental delay.

3-A-2 Effects of prostaglandin-E2 administration during critical period of mouse development on expression of Wnt-target genes

Ravneet Bhogal[1], **Christine Wong**[1], **Hongyan Li**[1], **Dorota Crawford**[1]
[1]York University

Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder caused by many genes in addition to environmental factors, which determine the broad severity of phenotype. The plasma membrane phospholipids serve as a supply of bioactive molecules such as prostaglandins E2 (PGE2) important for normal brain function. Abnormalities in lipid metabolism due to events that increase the level of PGE2 have been linked with malformations in the nervous system and ASD. Recent studies have also shown a cooperative regulation of PGE2 signalling with the wingless (Wnt) pathway in non-neuronal cells. Objectives: Our current study aims to investigate the role of PGE2, and its interaction with the wnt pathway in early neuronal development, in a mouse model. Methods: Wild-type mice administered with exogenous PGE2 during the critical period of development (embryonic day 11) were investigated for gene expression of Wnt-target genes. We tested the effects of PGE2 on brains derived from the embryonic days 16 and 19, and postnatal day 8. Results: Wild-type mice exposed to various doses of PGE2 also show differentially expressed Wnt- (Wnt-1, -2, -3a, -4)and Wnt-target (Mmp7, Fosl1, Enc1) genes. Of these, Wnt-2 has previously been implicated in autism. Conclusion: In this study, we found that using exogenous drugs to alter the PGE2 signalling pathway, caused changes in expression levels of crucial neurodevelopmental genes during early stages of brain development, which may give some insight to the pathology of ASDs.

3-A-3 Impaired neurogenesis in the aging forebrain: defining the kinetics and underlying mechanisms

Loïc Cochard[1], **Laura Hamilton**[1], **Sandra Joppé**[1], **Anne Aumont**[1], **Karl Fernandes**[1]

[1]University of Montreal

In the adult brain, the subventricular zone (SVZ) surrounding the lateral ventricles is the principle site of neural precursor proliferation and adult neurogenesis. SVZ neurogenesis plays an important homeostatic role for forebrain neuronal and glial cell populations. However, for reasons that remain poorly understood, forebrain neurogenesis is highly diminished in the aged brain, likely contributing to reduced cognitive plasticity and regenerative potential. In this work, we aim to better understand the mechanisms involved in aging-associated reductions in adult neurogenesis. We began by performing a meta-analysis of the literature to determine whether consistent patterns of aging-associated changes could be identified. While this analysis revealed some common patterns of observations, it also identified major gaps in our knowledge. To begin filling these gaps, we undertook several lines of investigation. First, to more clearly establish the kinetics of aging-associated changes in SVZ neurogenesis, we performed a detailed time-course experiment spanning across key adult ages. Second, we used a variety of markers to assess the possible involvement of senescence-associated processes. Third, using biochemical and immunohistochemical approaches, we investigated changes in intracellular signaling pathways associated with neurogenesis reductions. We ultimately aim to test whether modulation of these signaling pathways can inhibit or prevent aging-associated neurogenesis impairments. Supported by the Canadian Institutes of Health Research (CIHR).

3-A-4 STIM and store-operated calcium entry in the developing nervous system

Claire Hadrill[1]***,*** **Emily Ainslie**[1], **Camilla Mitchell**[1], **Robert Gasperini**[1], **Lisa Foa**[1]
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A key source of calcium within neurons is the endoplasmic reticulum (ER), the regulation of which, is poorly understood. The stromal interaction molecules (STIM1 and STIM2) are calcium-sensing proteins located in the ER membrane. STIM proteins interact with Orai proteins on the plasma membrane to initiate calcium influx and refill depleted intracellular calcium stores within the ER. STIM2 has been described as the "neuronal isoform" of the STIM family, although there has been much debate over its role in SOCE regulation. We have demonstrated that within the embryonic and adult nervous system, there is ubiquitous distribution of STIM1 and Orai1. STIM2 expression however is restricted to radial glia in the embryo and expression levels steadily decline during postnatal development. We have previously shown that STIM1 functions to mediate store-operated calcium entry (SOCE) in growth cones navigating in response to the guidance cues BDNF and Sema-3a (Mitchell et al., J. Neurochem., 2012). We now show that turning towards Netrin-1 also requires STIM1 and Orai1 expression (-6.2±1.5°, $p<0.0001$; 2.33±1.51°, $p<0.001$ respectively). Our data suggest that STIM1 and STIM2 play discrete cellular-specific roles in the developing nervous system.

3-A-5 Bcl-xL is a Critical Regulator of Apoptosis in Distinct Cell Populations throughout the Developing Nervous System

Lauren Fogarty[1], **Hilary Martin**[1], **Beibei Song**[1], **S. M. Mahmudul Hasan**[1], **Jieying Xiong**[1], **Jacqueline Vanderluit**[1]
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Neural precursor cells (NPCs) consist of a diverse population of neural stem cells, progenitor cells and neuroblasts. Although NPC diversity is determined by the stage of development as well as their location, less is known about the apoptotic signaling pathways that regulate this population. Here, we examined the role of anti-apoptotic Bcl-xL protein in promoting the survival of NPCs and newly differentiated neurons in the developing nervous system. Nestin mediated conditional deletion of Bcl-xL in the mouse embryonic nervous system revealed massive cell death in specific cell populations within the spinal cord, hind brain and cortex at distinctly different times during

development. Cell death is observed at the start of neurogenesis at embryonic day 11 (E11) in the spinal cord and hindbrain. In contrast, apoptosis is not observed in the cortex until neurogenesis is concluding at E17. To determine how Bcl-xL promotes cell survival in the developing nervous system, we are examining the expression profile of the pro-apoptotic Bcl-2 family members. This study will demonstrate the diversity of survival signaling pathways within the NPC population at different stages during embryonic development
Acknowledgements: This work was supported by an operating grant from the Canadian Institutes of Health Research and the Research and Development Corp. of Newfoundland and Labrador to JV. LF is supported by an NSERC Canada Graduate Scholarship.

3-A-6 The transcription factor MEF2 directs developmental visually driven functional and structural metaplasticity.

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Natural sensory input shapes both structure and function of developing neurons, but how early experience-driven morphological and physiological plasticity are interrelated remains unclear. Using rapid time-lapse two-photon calcium imaging of network activity and single-neuron growth within the unanesthetized developing brain, we demonstrate that visual stimulation induces coordinated changes to neuronal responses and dendritogenesis. Further, we identify the transcription factor MEF2A/2D as a major regulator of neuronal response to plasticity-inducing stimuli directing both structural and functional changes. Unpatterned sensory stimuli that change plasticity thresholds induce rapid degradation of MEF2A/2D through a classical apoptotic pathway requiring NMDA receptors and caspases-9 and -3/7. Knockdown of MEF2A/2D alone is sufficient to induce a metaplastic shift in threshold of both functional and morphological plasticity. These findings demonstrate how sensory experience acting through altered levels of the transcription factor MEF2 fine-tunes the plasticity thresholds of brain neurons during neural circuit formation.

3-A-7 Spinal Neuron Identity and Survival in the Absence of Neurosecretion

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Nervous system development is dependent upon the regulated secretion of morphogens, neurotrophins and neurotransmitters. Prior work shows that electrical activity influences neural circuit development by affecting gene transcription, neural patterning and axon guidance, though understanding of these effects has been limited by the imprecise nature of pharmacologically-induced electrical activity manipulations. The Munc18-1 protein is critical to neurosecretion and regulates the realease of neurotrophins and neurotransmitters. We examined development of the nervous system of mice lacking Munc18-1, allowing us to assay the role of patterned electrical activity and neurally-derived neurotrophin secretion in spinal neuron patterning and survival. We show that Munc18-1 mutants lack patterned neuronal activity in the spinal cord, but that surprisingly, molecularly-defined motor neurons and interneurons are generated normally. However, in Munc18-1 mutants there is a dramatic increase in activated caspase expression in motor neurons and interneurons. An accumulation of neurotrophin receptor in neuronal cell bodies can also be seen, suggesting impaired neurotrophin signalling. We also observe that Munc18 mutants have a normal response to peripheral, limb-derived neurotrophins, providing evidence for our woking hypothesis that there is a remarkable dependence of motor neurons and interneurons on central neurotrophic signals.

3-A-8 GABAergic signaling in Hippocampal Adult Neurogenesis: Examining the in-vitro Effects of Selective GABAAR agonists

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Adult neurogenesis (AN) in the mammalian hippocampus is a remarkable example of neural plasticity that occurs throughout life in distinct neurogenic microenvironments. One such region is the dentate gyrus (DG) in the hippocampus. Neural progenitor cells (NPCs) in the DG undergo a choreographed process while maturing into excitatory dentate granule cells (DGCs). Extrasynaptic GABAARs generate tonic depolarizing current in immature neurons, which is critical for progression of NPCs to integrated, electrophysiologically viable, adult DGCs. Activation via GABAARs exerts regulatory effects on of DGC proliferation, survival, and integration. Hippocampal slice-cultures were used to characterize the action of the compound 4,5,6,7-tetrahydroisoxazolo (5,4-c) pyridine-3-ol (THIP) and investigate δGABAAR influence on hippocampal AN. The selective GABA agonist, THIP, is a superagonist of δ-subunit GABAAR's (δGABAAR). Past experiments have shown THIP promotes increased neuronal survival and maturation in rat brain in vivo. Hippocampal cultures will help isolate the effects of THIP and δGABAAR on new neuron survival. Immunohistochemistry and confocal microscopy is used to quantify new neuron production and characterize differences between THIP and control conditions. We hypothesize that THIP promotes neuronal maturation and survival by a direct action in-vitro. Reduced neurogenesis impairs hippocampus-dependent learning and aberrant neurogenesis is involved in clinical conditions such as epilepsy. Understanding the influence of GABA may lead to new therapies for neurological diseases.

3-A-9 Sensory activity instructs neuronal morphogenesis in the awake brain

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During development, altering neurons' input or firing activity alters their growth and ultimate morphology. However, it remains unknown to what extent sensory experience actively instructs morphogenesis or if activity is simply permissive for normal neuronal growth. Using two-photon-guided single cell electroporation to label neurons with known receptive fields in the awake brain, we show that natural sensory stimulation alters dendrite growth in a manner dependent on neurons' evoked firing. We track these neurons throughout a period of sensory training, showing that specific dendrite growth patterns co-occur with specific forms of training-induced functional plasticity. We will also present data from ongoing experiments using random-access 3D two-photon microscopy to simultaneously image local dendritic calcium transients across neurons' entire dendritic arbor. Our results support an instructive role for neuronal firing and local dendritic signalling in developmental dendritogenesis, shaping neuron morphology according to an organism's specific experiences.

3-A-10 Electrical stimulation facilitates diabetic peripheral nerve regeneration through the PI3-K signaling pathway

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Peripheral nerve regeneration is compromised in diabetes mellitus. In nondiabetic nerves, a short extracellular electrical stimulation (ES) paradigm applied immediately after nerve injury augments axon regeneration. The potential impact of this intervention in diabetic nerves is uncertain. A cohort of 2 month type 1 diabetic (STZ induced) mice was divided into ES and sham stimulation (SS) groups following sciatic crush. ES (20Hz, 3V, 1h) or SS was applied to the proximal injured nerves. In separate experiments in vitro, neurite outgrowth of isolated adult diabetic sensory neurons was measured following an ES paradigm (200mV, 20Hz, 1h) applied through a multi-electrode array.

Diabetic mice were hyperglycemic and gained less weight than nondiabetic controls. ES improved recovery of motor electrophysiology and mechanical sensation at 28 dpi. The density of regenerating intraepidermal fibers and tibial myelinated axons were higher with ES. In vitro, stimulated diabetic neurons showed higher neurite outgrowth than controls. In nondiabetic neurons, we explored novel mechanisms of the benefits of ES. Isolated sensory neurons imaged by two photon microscopy had increases in intracellular calcium in response to ES, and the ES induced growth was blocked by a PI3-K inhibitor but not Nicl2. Following ES of nondiabetic nerves in vivo, PTEN expression was reduced, with rises in pAkt and ps6k in ipsilateral DRGs. Extracellular ES facilitates robust nerve regeneration in diabetic animals. Mechanisms include facilitation of PI3-K signaling by PTEN suppression. [Supported by CIHR, AIHS].

3-A-11 Intermittent physical stress in adolescence increases risk-taking behaviour and pre-limbic pyramidal cell complexity in adult rats.

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Our previous research demonstrates that exposure to intermittent physical stress (IPS) during early vs. mid-adolescence differentially alters rats' anxiety-like behaviour in adulthood. Here, we exposed rats to IPS during mid-adolescence (PD35-46) and tested them in adulthood (~PD72) using the elevated plus maze. As in our previous work, we observed marked increases in open-arm exploration in the stress rats relative to controls. This reaffirms our earlier suggestion that stress during mid-adolescence increases risk-taking behaviour in adulthood. In addition, Sholl analysis conducted on pyramidal neurons (layer V) of the medial prefrontal cortex (mPFC) suggest trend-like increases in apical dendrite complexity; this trend was particularly evident in male, but not female, rats. While preliminary, it appears that the lasting impact of stress during mid-adolescence on risk-taking behaviour might be due, at least in part, to stress-induced changes in the complexity of apical dendrites of pyramidal cells (layer V) in the mPFC.

3-A-12 AP-2α and AP-2β: redundant partners in the postnatal mammalian retina

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The Activating Protein-2 (AP-2) transcription factors are a family of genes playing essential roles in the development of the eye. Previous studies from our lab have shown that the AP-2α germ-line knockout (KO) mice display a variety of retinal defects. Since these KO mice died prenatally, retinogenesis could not be examined past embryonic day 16.5. Expression studies have shown that multiple AP-2 family members are expressed in the retina. For example, AP-2α is specifically expressed in postmitotic amacrine cells, while AP-2α and AP-2β are co-expressed in developing horizontal cells. However, conditional deletion of either gene does not result in observable retinal defects. Thus, using Cre-loxP, double mutants lacking both AP-2α and AP-2β in the developing retina were generated in order to examine their potentially redundant roles in the development of the neural retina. Morphologically, double AP-2α/AP-2β retinal mutants displayed unilateral retinal dysplasia in the peripheral retina, including an inside-out retina, thick and twisted retina with a pigmented layer within the twist, and retinal whorls. These double mutants also displayed abnormalities in the inner nuclear layer that were not present in the single gene mutants. A loss of horizontal cells was observed using markers such as LIM1, Calbindin and neurofilament medium chain. These data demonstrate the potential redundant roles of AP-2α and AP-2β in neural retinogenesis and suggest that, together, these genes have an intrinsic role in the development of horizontal cells and they impact retinal structure.

3-A-13 NCK Proteins are Critical for Axon Guidance During Development

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Loss of Nck adaptor proteins in the nervous system leads to axon guidance defects in the cortico-spinal tract and changes in local spinal circuits affecting the normal output of the central pattern generator. Since Nck proteins are widely expressed in the nervous system we were interested to see if they had more global effects on axon guidance. Here we examined the developing cranial nerves by staining Nck deficient and control embryos with anti-neurofilament. No obvious differences in the development of the facial or trigeminal nerves were noted; however, guidance defects in the vagal nerve including misprojections into dorsal tissue and defasciculation were seen. Since NCK proteins function as molecular scaffolds and have been shown in vitro to connect a number of guidance receptors including the netrin receptor DCC, we also investigated the in vivo function of NCK in DCC sensitive pathways. Interestingly, NCK mutant mice show a significant reduction in commissural axons crossing at the floor plate. Together, these studies provide further evidence for the role of the NCK proteins in neural development and highlight a specific role for NCK in the guidance of DCC positive axons.

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

3-B-14 Loss of Connexin36 protects hippocampal neurons from excitotoxic induced cell death

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Connexins (Cx) are a family of proteins that form the structural units of gap junction channels (intercellular communication) and can form single membrane channels in non-junctional membranes. Of the 21 known connexins three are expressed by neurons, Cx36, Cx45, and Cx57. Connexin36 is ubiquitously expressed by neonatal hippocampal neurons in mice. In adult rodents transcript and protein has only been reported in parvalbumin-positive interneurons. Conversely, in rats, Cx36 mRNA is detected in interneurons and CA3 pyramidal cells throughout postnatal development. The loss of Cx36 from adult rodents, presumably interneurons, has been shown to abolish synchronous electrical coupling. Here, we investigate the role of Cx36 in kainic acid-induced hippocampal excitotoxicity. As expected, CA3a/b pyramidal neurons undergo delayed excitotoxic death in Cx36 / mice. In Cx36-/- mice post injury, neurons of the hippocampus do not succumb to excitotoxic death. We identified Cx36 using in situ hybridization, immunofluorescence, and western blotting, along with functional behavioural and electrophysiological assessments post injury. Together, these data demonstrate the role of Cx36 in excitotoxic dependent cell death, identifying this protein as a potential target for mediating excitotoxic injury.

3-B-15 The seasonal reversal in GABA sensitivity of Lymnaea Stagnalis pedal ganglia neurons is photoperiod dependent

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GABA is the primary inhibitory neurotransmitter in the mature mammalian central nervous system. Activation of the GABAA receptor results in Cl^- ion influx and neuronal inhibition. The Cl^- ion gradient is established through the relative expression and efficacy of the $K+/Cl^-$ co-transporter 2 (KCC2) and the $Na+/K+/2Cl^-$ co-transporter 1 (NKCC1), which establishes the GABA reversal potential (EGABA) and determines whether GABA is excitatory or inhibitory. The role of GABA within the snail central ganglion consists of contradictory reports, citing both inhibitory and excitatory effects. Our lab has demonstrated a seasonal shift in the GABA response, with excitatory responses during the

winter and inhibitory responses during the summer. It was the objective of this study to determine whether the changes in photoperiod associated with seasonality were responsible for this seasonal shift in GABAergic polarity. Using intracellular sharp recordings from cluster F neurons within the pedal ganglia of the central ganglion we determined that snails exposed to a 8h:16h light dark (LD) cycle exhibited more than a two fold increase in action potential frequency (APf) and a GABA-mediated depolarization of membrane potential (Vm). Conversely, in snails exposed to a 16h:8h LD cycle exhibited more than a 50% decrease in APf and GABA application induced a hyperpolarization of Vm. We conclude that the seasonal shift in GABA response results from a shift in EGABA which is photoperiod dependent and is likely mediated through a KCC2/NKCC1 mechanism.

3-B-16 Intracellular Pannexin1: investigating a novel localization and mode of trafficking with implications for neuronal viability

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Pannexin 1 (Panx1) is a large pore ion and metabolite-permeable channel. It is expressed abundantly in the brain and has received considerable attention in molecular stroke research. Panx1 is activated by elevated extracellular potassium, oxygen-glucose deprivation (OGD), and caspase-3 mediated cleavage of its C-terminus, stimuli that are present in the post-stroke brain. Current models point primarily to a role for plasma membrane Panx1 in mediating neuron and astrocyte vulnerability to these stimuli. However, in several different cell types, we noted intracellular expression of Panx1 in a large proportion of cells and this localization is increased by stroke-related stimuli. We confirmed the precise localization of Panx1 using well-characterized intracellular membrane marker protein antibodies using confocal microscopy and subcellular fractionation. In parallel, using an unbiased proteomic approach we identified several putative protein interactors. We discovered that a subset of these take part in specific, highly regulated intracellular protein trafficking pathways. As the aforementioned stimuli have been shown to modulate full-length Panx1 surface expression and channel activity, we hypothesize that the intracellular trafficking of Panx1 may regulate the response of Panx1 to these stimuli, and thus the pathophysiological consequences of Panx1 activation. Taken together the data we will present have important implications for the role of Panx1 in the regulation of cell viability following stroke.

3-B-17 Functional organisation of VIPergic inhibitory microcircuits in the CA1 hippocampus

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Information processing by neuronal circuits depends on the dialogue between principal cells and local GABAergic interneurons (INs). Intriguingly, a population of INs specialized in innervating other GABAergic cells exists in the CA1 hippocampus; however their physiological properties, connectivity and function remain unknown. Given that most interneurons-specific interneurons (ISIs) express vasoactive intestinal polypeptide (VIP), here we used a VIP-eGFP mouse model and a combination of dual patch-clamp recordings and cellular imaging to study the functional organisation of VIPergic inhibitory microcircuits in the CA1 hippocampus. Four types of VIP INs have been identified on the basis of physiological and anatomical properties, molecular expression profiles, and postsynaptic targets. Apart from the VIP/cholecystokinin co-expressing basket cells (Type I), which contacted pyramidal neurons, VIP-positive INs innervated preferentially other INs. Type II INs contacted GABAergic cells in the stratum radiatum and lacunosum-moleculare. Type III and IV INs innervated distinct types of INs in the stratum oriens/alveus (O/A), with a preferential targeting of oriens-lacunosum moleculare cells. Synapses formed by VIP cells exhibited both input- and

target-specific properties. Interestingly, type IV INs, with a soma located in O/A, also projected to the subiculum and were interconnected by GABAergic synapses and gap junctions. Therefore, the latter subtype of VIP-expressing INs can be a part of the long-range projecting INs specialized to coordinate the hippocamposubicular circuit.

3-B-18 Optogenetics approach to investigate the role of interneurons in seizure propagation in an in vitro and in vivo model of epilepsy

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Using an optogenetic approach, our aim was to investigate the role of inhibitory interneurons in shaping seizure like events (SLEs). Electrophysiological experiments were performed on a transgenic strain of mice that express channelrhodopsin-2 in interneurons via the vesicular GABA transporter promoter. As such, interneurons in these mice depolarize and fire action potentials when exposed to 473nm light. Accordingly, a 30ms pulse of light induced local field potentials (LFPs) in the cortical layers that were augmented with application of 4-aminopyridine (4-AP, 100uM). GABAA/B blockers, bicuculline methiodide (BMI, 10μM) and CGP 55845 (CGP, 4μM), diminished the response. We found that bath application of 4-AP induced spontaneous SLEs, while light induced SLEs displayed strong temporal correlation to the light pulses (circular variance (CV)=1.6x10-6; n=35). The addition of BMI abolished the SLE-light pulse correlation (CV=0.72; n=38). Similar findings were found in parallel with an in vivo 4-AP model of epilepsy, where light pulses were highly correlated with SLE initiation. The in vivo model further showed that interneuronal activation with light stimuli (3s, 6Hz) regularized seizure activity, and concentrated power within the theta frequency range. Our preliminary findings suggest that synchronous activation of interneurons during hyperexcitable states can trigger SLEs and modify any ongoing SLEs. Interneuronal synchrony thus appears to be a critical component in the propagation of epileptiform activity in the 4-AP model of epilepsy.

3-B-19 Anti-inflammatory effects of statin treatment in primary cultured microglia

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As the primary immune cells of the central nervous system, microglia play critical roles in defence against foreign agents and clearance of cellular debris, as well as a myriad of lesser explored roles in development, homeostatic regulation, and synaptogenesis. In some neurodegenerative conditions inflammatory activation of microglia can exacerbate the underlying disease state, accelerating or causing further damage to afflicted tissue. The statin class of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have been proposed to have anti-inflammatory and neuroprotective effects in addition to their well-characterized effects at lowering serum cholesterol. In primary culture microglia, simvastatin treatment decreased the secretion of inflammatory mediators including nitric oxide and cytokines, while promoting cellular survival and inhibiting phagocytosis in both resting microglia and those exposed to a potent inflammatory stimulus. While these effects were correlated with changes in cellular cholesterol levels, direct manipulation of cholesterol increased the inflammatory response of microglia and recovery of cholesterol levels in simvastatin treated cells failed to restore normal reactivity. These results suggest simvastatin inhibits phagocytosis and elicits a less inflammatory phenotype through cholesterol-independent mechanism and may be protective in neurodegenerative disorders or ischemic stroke.

3-B-20 Synaptotagmin I is expressed at a GABA/glycine/glutamate-releasing central synapse, independent of vesicular glutamate transporter 3 expression

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The continuing discovery of synapses that use multiple transmitters has raised new questions about synaptic transmission, vesicular phenotype, and protein targeting. During an early period of circuit refinement, synaptic terminals in the brainstem MNTB-LSO pathway release the three classic small amino acid transmitters: GABA, glycine, and glutamate. Slice physiology strongly suggests that these terminals contain two vesicle populations, one a GABA- and glycinergic population and the other a glutamatergic population characterized by expression of vesicular glutamate transporter 3 (VGLUT3). We recently found that the immature MNTB-LSO synapse expresses both synaptotagmin 1 (Syt1) and synaptotagmin 2 (Syt2). As Syt1 and VGLUT3 exhibit similar spatial and temporal expression patterns and colocalize in MNTB terminals, the working model for this synapse posits a population of vesicles uniquely characterized by co-expression of VGLUT3 and Syt1. This model raises the question of whether one of these synaptic proteins might influence expression and/or trafficking of the other protein. We asked whether VGLUT3 is necessary for Syt1 expression in MNTB synaptic terminals by immunostaining for Syt1 in tissue from both wildtype and VGLUT3 knockout mice. We found that Syt1 was expressed at normal levels, and that Syt1 protein was present in the MNTB-LSO synaptic terminals, regardless of VGLUT3 expression. Thus, in the MNTB-LSO pathway, VGLUT3 expression is not necessary either for Syt1 expression or for targeting of Syt1 to synaptic terminals.

3-B-21 Neurons actively maintain the molecular program of astrocytes in the adult brain

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Interactions between neurons and glia are important for proper CNS function, including synaptic development and plasticity. However, the inter-dependency of these cells types in the adult brain remains to be fully understood and the identity of the molecular cues and receptors that enable neuron-astrocyte communication remain poorly described. Here, we have uncovered that neurons in the adult brain signal to astrocytes using the well-known developmental morphogen Sonic hedgehog (Shh). Using a Cre-Lox reporter system we have found that Shh is expressed in discrete populations of neurons of the cerebellum in vivo, including granule cells (GCs) and Purkinje cells (PCs). By immunofluorescence, we localized the Shh signaling components Smoothened (Smo) and Patched2 in Bergmann glia (BG), the astrocytes of the cerebellum that modulate glutamatergic transmission onto PCs. In vitro, Smo and Ptch2 are expressed on the cell surface of cerebellar astrocytes. Treatment of cerebellar astrocytes with a Shh peptide or the Smo antagonist up-regulates and down-regulates Shh pathway components, respectively, indicating that cerebellar astrocytes are responsive to Shh. We are currently investigating a role of Shh in cerebellar function in vivo through conditional removal Smo, a key transducer of Shh signaling, from BG in adult mice. We found coordinated changes in gene expression and cell morphology of BGs, indicating that Shh is necessary to maintain the distinct phenotype of BGs. Our results indicate that neurons may play an active role in specifying glial properties in the adult brain.

3-B-22 A non-canonical effector of cAMP-dependent mossy fiber LTP in the hippocampus

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Neurotransmission between dentate granule neurons (mossy fiber axons) and hippocampal CA3 pyramidal neurons features robust long-term potentiation (LTP), expressed as a persistent increase in presynaptic release probability. cAMP signaling has been implicated in the mechanisms of LTP expressed in the presynaptic terminal. The

classic mediator for the actions of cAMP is protein kinase A (PKA), the activation of which results in enhanced synaptic release of glutamate. A new downstream target of cAMP, the guanine-nucleotide exchange factor Epac, has been linked to an alternate PKA-independent signaling pathway. The Epac2 isoform is enriched in the brain with expression particularly high in the dentate gyrus and CA3 regions of the hippocampus. We investigated whether this non-classical target of cAMP plays a role in mossy fiber synaptic plasticity. In whole-cell electrophysiological recordings from CA3 neurons in hippocampal slices obtained from Epac2-/- or Epac2 / (wild type) littermate mice, we found that basal synaptic transmission and short-term plasticity were not altered by the loss of Epac2. However, mossy fiber LTP was significantly impaired in Epac2-/- mice, using either tetanic or chemical induction of LTP. Western blot analyses of large mossy fiber synaptosomes revealed that expression of the synaptic proteins Rab3A and CASK was significantly reduced in samples from Epac2-/- mice. These data provide evidence of a significant role for Epac2 activity in mossy fiber LTP, and as a possible mediator of neural activity underlying hippocampal-dependent memory.

3-B-23 Selective activation of KCa3.1 and CRAC channels by P2Y2 recptors promotes Ca2+ signaling, store refilling and migration of rat microglial cells

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ATP released from damaged neurons can activate ionotropic and metabotropic purinergic receptors and act as a chemoattractant for microglia. Metabotropic P2Y receptors evoke a Ca2 rise via release from intracellular Ca2 stores and store-operated Ca2 entry, and some have been implicated in microglial migration. This Ca2 rise is expected to activate small conductance Ca2 -dependent K (SK) channels. We previously found that SK3 and KCa3.1 (SK4) are expressed in rat microglia and contribute and contribute to LPS-mediated activation and neurotoxicity. However, neither current has been studied. We hypothesized that, rather than responding only to Ca2 , each channel type might be coupled to different receptor mediated pathways. Here, our objective was to determine whether the channels are differentially activated by P2Y receptors, and if so, whether they play differing roles. We used primary rat microglia and a rat microglial cell line (MLS-9) in which riluzole robustly activates both SK3 and KCa3.1 currents. Using electrophysiology, Ca2 imaging and pharmacology, we show selective functional coupling of KCa3.1 to UTP-mediated P2Y2 receptor activation. KCa3.1 current is activated by Ca2 entry through Ca2 -release-activated Ca2 (CRAC/Orai1) channels, and both CRAC and KCa3.1 channels facilitate refilling of Ca2 stores. Unexpectedly high Ca2 was required for KCa3.1 channel activation, and we present evidence for a close physical association of the two channel types. Finally, migration of primary microglia was stimulated by UTP and inhibited by blocking either KCa3.1

3-B-24 Changes in the electroretinogram of AP-2α and AP-2β double knockout mice

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PURPOSE: The Activating Protein- 2 (AP-2) family of transcription factors have been shown to be important in neural retinogenesis. We believe AP-2α and AP-2β have redundant roles and may regulate the development of horizontal cells and cholinergic amacrine cells. The full-field electroretinogram (ERG) is a mass electrical response to photic stimuli, the components of which are derived from different retinal cells. The purpose of this study was to evaluate the physiological function of the retina using ERG anaylsis in animals missing the AP-2α and AP-2β genes. METHODS: To generate double AP-2α/AP-2β retinal mutants, Pax6 α-Cre mice were used to conditionally delete one floxed allele of AP-2α and AP-2β at E10.5. The second allele of AP-2α/AP-2β was deleted as a germ-line knockout. Full-field ERGs were recorded from dark adapted (12 hours),

anesthetized (Avertin) 6wk old mice. The amplitude of the a-wave (outer retina), b-wave (partially attributed to the inner retina), and oscillatory potentials (OPs; attributed to the inner retina) were analyzed. RESULTS: Data from age matched (6wk old) WT and AP-2 deleted mice showed that the amplitude of the a-wave was similar (p=0.194) but there was a significant 45% decrease (p=0.05) in the amplitude of the b-wave. The number and amplitude of the OPs were also reduced in AP-2 deleted mice. CONCLUSION: These findings suggest that that the double AP-2α/AP-2β retinal mutants have decreased inner retinal function which is consistent with observed morphological changes in laterally conducting retinal neurons after AP-2α/AP-2β deletion.

3-B-25 Dynamic regulation of synaptic strength onto 5-HT neurons by antidepressants

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Antidepressants are generally believed to exert their clinical efficacy by enhancing serotonin (5-HT) transmission. However, they do so with a delay of several weeks that broadly matches the delay of therapeutic benefits in humans. For instance, sustained administration of selective 5-HT reuptake inhibitors (SSRIs) suppresses in the first few days the firing activity of 5-HT neurons in the dorsal raphe nucleus (DRN), thereby severely hampering the increase of 5-HT in target regions. Remarkably, the firing activity of 5-HT neurons gradually recovers over the time course of treatment. We hypothesized that a homeostatic-like upregulation of excitatory synapses onto 5-HT neurons might, at least in part, account for this recovery. We thus treated rats with the SSRI citalopram and monitored excitatory synaptic function onto 5-HT neurons using ex vivo whole-cell electrophysiological recordings. A 2 day treatment with citalopram induced a robust reduction in the function of both AMPA and NMDARs. These synaptic adaptations were mediated by both pre- and postsynaptic mechanisms, without any apparent changes in AMPAR subunit composition. Remarkably, this SSRI-induced depression in synaptic transmission was transient since excitatory drive was enhanced by 7 days of SSRI treatments. Altogether, these results document a dynamic and unsuspected regulation of glutamatergic synapses onto 5-HT neurons by SSRIs. Elucidating of the cellular and molecular mechanisms driving this synaptic plasticity might identify novel pharmacological targets to shorten the delay of antidepressant action.

3-B-26 Vesicular glutamate transporter 3 (VGLUT3) does not synergize GABA/glycine release at immature inhibitory synapses in the auditory brainstem

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In the immature auditory brainstem, expression of the vesicular glutamate transporter VGLUT3 allows glutamate release at GABA/glycinergic terminals from cells of the medial nucleus of the trapezoid body (MNTB) within the lateral superior olive (LSO). Normal circuit refinement in the MNTB-LSO pathway requires VGLUT3 expression and is driven by patterned spontaneous activity. VGLUT3 could support activity-dependent plasticity through activation of postsynaptic NMDARs or through "vesicular synergy," by promoting vesicle filling. Expression of VGLUT3 is known to allow NMDAR activation on LSO cells, whereas the synergistic influence of VGLUT3 has been demonstrated at cholinergic and serotonergic terminals. Whether VGLUT3 can also synergize GABA/glycine loading at inhibitory synapses has remained an open question To answer this question we used whole-cell patch in brainstem slice to compare short-term plasticity in VGLUT3 wildtype, heterozygous, and knockout mice. We found no effect of genotype on paired-pulse ratios (n=73), recovery from paired-pulse depression (n=21), or miniature inhibitory events (n=13). Our results suggest that VGLUT3 does not synergize the filling of GABA/glycinergic vesicles in the MNTB-LSO pathway; they corroborate previous

work suggesting that VGLUT3 and the vesicular inhibitory amino acid transporter (VIAAT) are trafficked to distinct vesicle populations in MNTB terminals; and they are consistent with a model in which glutamate release and NMDAR activation are required for developmental refinement in an inhibitory circuit.

3-B-27 The effects of toluene on inhibitory synaptic transmission in the cerebellar cortex

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Inhalant abuse is a growing concern for children and early adolescents. Toluene is the chief constituent responsible for the euphoric, intoxicating effects of inhalants. Exposure to toluene results in marked impairments in motor function, including a loss of coordination and balance. These impairments are characteristic of cerebellar dysfunction. Previous research has found that toluene increases extracellular gamma-aminobutyric acid (GABA) levels in rodents, but the cellular mechanism(s) is unknown. To address this, we have used patch clamp electrophysiology on parasagittal cerebellar slices obtained from Long-Evans rat pups postnatal days 12-28. Whole cell voltage clamp recordings were obtained from Purkinje cells to monitor the effects of toluene on inhibitory synaptic transmission. Application of toluene dose-dependently enhanced both the frequency and amplitude of inhibitory postsynaptic currents (IPSCs). Experiments in progress are addressing several possible mechanisms that may account for the observed changes in IPSCs. Identification of the mechanisms accounting for altered cerebellar functioning and cerebellar-dependent behaviours may speak to future therapeutic interventions in cases of toluene abuse.

3-B-28 GSK3 affects Arc protein expression in primary neuronal culture. Possible implications for synaptic plasticity

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GSK3 alpha/beta (Glycogen Synthase Kinases alpha/beta) are serine/threonine kinases ubiquitously expressed in the nervous system. GSK3's appear to be critical for LTD formation, and overactivation of GSK3 inhibits LTP expression. Here we report that GSK3 regulate expression of Arc/Arg3.1 protein (Activity Regulated Cytoskeleton Associated Protein/Activity Regulated Gene 3.1), involved in diverse forms of synaptic plasticity, including LTP, LTD and homeostatic plasticity. We hypothesize that Arc could be one of the putative GSK3 effectors in neurons. The combination of low dose NMDA and GSK3 inhibitors up-regulated Arc expression at the protein but not at the transcriptional level. Recombinant Arc protein is phosphorylated in vitro by GSK3 beta. Currently, we are characterizing the mechanism of GSK3-dependent Arc degradation. We also observed that the co-treatment of neurons with GSK3 inhibitors and NMDA altered dendritic spine morphology, e.g. 6 hours exposure to GSK3 inhibitors decreased average dendritic spine width and the co-application of NMDA produced additional spine thinning. We also evaluated the effect of GSK3 inhibition on Arc expression and subcellular distribution in in vitro chemical LTP and LTD models. Currently, we are employing shRNA technology to determine if Arc contributes to the observed alterations in dendritic spines morphology and what is the role of GSK3- dependent Arc degradation in different forms of synaptic plasticity.
Supported by 7FP EU grant 223276 "NeuroGSK3" and 2011/01/B/NZ3/05397 grant from National Science Centre

3-B-29 Characterization of dendritic spines in rat spinal cord lamina I and II neurons

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Dendritic spines serve not only as points of contact for presynaptic axons to communicate with the

postsynaptic neuron, but also as computational units critical to synaptic plasticity. In the brain there are well-characterized differences in the presence and density of spines across different types of neurons. Here we studied dendritic spines in neurons in the superficial layers of the spinal dorsal horn. We used acute spinal cord slices from adult rats and filled neurons in lamina I and II with Lucifer yellow through a patch-clamp pipette. Slices were fixed with PFA, and imaged using 2-photon microscopy to build 3D reconstructions of filled neurons. Slices were then labelled for CGRP, IB4 and NeuN to confirm laminar localization. 21 of 23 neurons injected with Lucifer yellow were adequately filled and included for analysis. Of 11 lamina I neurons 6 had spines, while 9 of 10 lamina II neurons were spiny. On average, the density of spines in spiny lamina II neurons was greater than that of spiny lamina I neurons. Lamina I neurons were classified morphologically as fusiform (n=6), pyramidal (n=3) or multipolar (n=2). We found that one-third of fusiform, two-thirds of pyramidal and both multipolar neurons were spiny. Moreover, spine density of multipolar cells was greater than that of fusiform or pyramidal cells. These results suggest that in the superficial dorsal horn there are laminar and morphological cell-type differences in spine density. These differences may contribute to functional differences across populations of lamina I and II neurons.

3-B-30 DCC expression by neurons regulates synaptic plasticity in the adult brain

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The transmembrane protein DCC and its ligand netrin-1 regulate synaptogenesis during development but their function in the mature CNS is unknown. Given that DCC promotes cell-cell adhesion, is expressed by neurons, and activates proteins that signal at synapses, we hypothesized that DCC expression by neurons regulates synaptic function and plasticity in the adult brain. We report that DCC is enriched in dendritic spines of pyramidal neurons in wild-type mice and demonstrate that selective deletion of DCC from neurons in the adult forebrain results in the loss of LTP, intact LTD, shorter dendritic spines, and impaired spatial and recognition memory. LTP induction requires Src activation of NMDA receptor function. DCC deletion severely reduced Src activation. We demonstrate that enhancing NMDAR function or activating Src rescues LTP in the absence of DCC. We conclude that DCC activation of Src is required for NMDA receptor-dependent LTP and certain forms of learning and memory.

3-B-31 Developmentally-Regulated Dendritic Calcium Signaling in CA1 Pyramidal Neurons

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During postnatal development, rodent hippocampal CA1 pyramidal cells (PCs) undergo robust dendritic growth accompanied by a significant increase in the number of synapses. These events contribute to the establishment of the neural circuitry of the mature hippocampus. Here, we describe calcium signaling features of CA1 PC dendrites that are sharply regulated during postnatal development and show that synapse maturation is under strong spatial regulation. Using whole-cell electrophysiology with 2-photon calcium imaging and glutamate uncaging in acute hippocampal slices, we have characterized calcium dynamics from >300 dendritic spines from >100 dendrites. We found that single-synapse activation triggered bidirectionally propagating dendritic calcium waves which invaded neighbouring dendritic spines. These calcium waves were restricted to early postnatal development and were dependent on NMDAR activation and ryanodine-sensitive intracellular calcium stores. Modeling results suggested that these calcium dynamics impart spatial attributes to the plasticity

mechanisms that drive synapse maturation during this critical ontogenic period. To test this prediction, we mapped functional synapse development by probing the AMPAR and NMDAR content of neighbouring spines. We found that synapse maturation occurs in a spatially clustered manner along dendritic segments. Together, our results reveal features of CA1 PC dendrites that are regulated during postnatal development which may have implications for neurodevelopmental disorders such as schizophrenia and autism spectrum disorders.

3-B-32 Severe hypoglycemia in juvenile diabetic rats: presence and severity of seizures predictive of mortality

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It is well accepted that severe hypoglycemia is a major limiting factor in the management of diabetes resulting in brain dysfunction and seizures. However, the effects of the seizures and treatment strategies have yet to be elucidated, particularly in juveniles. Here we establish a model of severe hypoglycemia and seizures in juvenile diabetic rats. Diabetes was established in post-weaned 22-day-old rats by streptozotocin (STZ; 80mg/kg) intraperitoneal (IP) injection. After a week, severe hypoglycemia was induced by insulin IP (15U/kg) in fasted (14-16 hours) diabetic (STZ) and non-diabetic (CON) animals. Experiments were video-monitored and seizures scored to quantify behaviour. Seizures occurred in 86% of STZ and 100% of CON rodents that reached hypoglycemia (defined as <3.5 mM blood glucose). The blood glucose thresholds for seizure onset were not significantly different between these groups; STZ: 1.8±0.2 mM, CON: 1.6±0.1 mM. Mortality in non-seizing animals was 0%, compared to those that seized (STZ: 33%, CON: 42%; $p<0.05$). Surviving animals exhibited a significantly reduced number of seizures in both CON and STZ groups ($p<0.001$). Treatment with anticonvulsants and glucose at seizure onset was significantly more successful at ameliorating seizures than glucose alone but did not improve mortality, as subclinical seizures may be present. This model of hypoglycemia and seizures in juvediabetic rats provides evidence that severe hypoglycemia (<2.0mM) is a necessary precondition for seizures, with mortality only occurring in the animals that exhibited seizures.

3-B-33 A Computer Model of Neuronal Growth and Migration in the Nigrostriatal Pathway

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Agent based models can provide novel insights into transplant and cell replacement therapies in degenerative states such as Parkinson's Disease. An agent-based computer model is constructed to represent migration and differentiation of neural stem cells in the nigrostriatal pathway. Experimentation on this model reveals that glial growth influences the trajectory of neurons to the striatum. The model incorporates differentiation, proliferation and migration behaviour by formulating a series of commands which can then be modified and quickly adapted to predict in-vivo conditions of varying signalling factor concentrations in the substantia nigra and striatum. The findings developed here supplement current cell-culture and in-vivo experimental methods and provide novel insights into neural stem cell growth and migration behaviour. Researchers can potentially use this model to guide neural stem cell implantation for the treatment of Parkinson's Disease.

3-B-34 Spine Synapse Density is Reduced in the Dentate Gyrus but not in the CA3 Subfield of the Hippocampus Following Castration in Male Non-human Primates

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Gonadal hormones have neuroplastic effects on the hippocampus, resulting in changes in cognitive ability. Androgens have been shown to produce mixed effects on hippocampal-based cognitive function in males. In the past, it has been shown that orchidectomy drastically decreases spine synapse density in the CA1 subfield of the hippocampus. However, the results of recent studies suggest that the effects of androgen are variable in the different areas of the hippocampus. Therefore, we sought to determine the effect that orchidectomy (1 month) has on synapse density in the stratum moleculare of the dentate gyrus (DGsm), and the stratum radiatum of the CA3 (CA3sr) subfield of the hippocampus in young adult male St. Kitts vervet monkeys (Chlorocebus aethiops sabaeus). The synapse density was significantly lower in castrated animals versus control animals in DGsm, but not in CA3sr. These results support our hypothesis that castration does not ubiquitously decrease synapse density in the hippocampus, since CA3 is relatively spared compared to CA1 and the dentate gyrus. As the primate model used in this study has similar hippocampal structure to that of a human, these findings suggest that androgens are important to maintenance of normal hippocampal structure, but that compensatory changes may occur to reduce synaptic loss following androgen deprivation. These findings may also help to resolve why castration has not been shown to consistently impair performance on tasks that assess hippocampal-based cognitive ability in males. [Supported by NIH ES017013 and NSERC 197293-2007].

3-B-35 Src is required for the induction of long-term depression of synaptic transmission in the CA1 region of the hippocampus in aged animals

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Long-term depression (LTD) is a principal form of persistent synaptic plasticity in the mammalian CNS. In this study, we examined LTD at the Schaffer Collateral (SC) - CA1 synapses in the hippocampal slices obtained from aged wild-type (WT) and Src null mice. Acute hippocampal slices were subjected to electrical stimulation of the SC input to CA1. The slope between the 10% to 60% of the field excitatory post-synaptic potential (EPSP) rising phase was used to assess changes in the strength of synaptic transmission. Three trains (900 pulses, 1 Hz each) separated by 2 episodes of 10 minute, 0.1 Hz stimulation were delivered to the SC in order to induce LTD. In WT mice, 60 min after delivering the third train, we found a 35.1±1.1% reduction (n=23, $p<0.05$) in fEPSP slope. At the same timepoint, in experiments with ACSF supplemented with 100 µM D-APV, a competitive N-Methyl-D-Aspartate receptor (NMDAR) antagonist, no statistically significant depression of synaptic transmission was observed (difference = 1.1±3.5, p=0.38, n =13 slices). In other experiments, we found in Src null mice that at 60 min following the final stimulus train there was no significant change in fEPSP slope respect to baseline (difference = 0.2±1.3, p=0.55, n =18 slices). Together, we conclude that LTD in the hippocampal CA1 of aged mice is NMDAR-dependent and requires a functional copy of the Src gene. This robust form of LTD in aged animals may provide insight into the pathophysiological basis of mental disorders including Alzheimer's disease, depression, schizophrenia, and others.

3-B-36 Investigating the Role of Transient Receptor Potential Melastatin Channel-2 in Microglia

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TRPM2 has previously been implicated in mediating neuronal cell death. However we have found that TRPM2 is highly expressed in microglia. Specifically, our study shows that TRPM2 transcript is differentially expressed between cell types: present only in microglia but not cortical neurons or astrocytes. A recent study has shown that TRPM2 mRNA expression is upregulated in parallel with microglia activation after focal ischemia. Using primary microglial cells isolated from TRPM2 knockout mice the current study aims to investigate

how the activation of TRPM2 in microglia plays a role in the brain's response to oxidative stress.

3-B-37 The role of Disrupted-in-Schizophrenia 1(DISC1), a key risk factor in major psychological disorders, in hippocampal synaptic plasticity and cognition.

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Schizophrenia is a severe psychological disorder that affects about 1% of the population. One of the key characteristics of this disorder is a deficit in cognitive functions such as learning and memory. Synaptic plasticity is a feature of the brain that is believed to be the basis for learning and memory and is represented by changes in synaptic strengths between neurons, termed potentiation. Disrupted-in-Schizophrenia 1 (DISC1) has emerged as a strong genetic risk factor for psychological disorders such as schizophrenia, bipolar disorder, and major depression. The DISC1 protein consists of 854 amino acids and is known to interact with many proteins including Kalirin-7 (Kal-7), phosphodiesterase 4B (PDE4B), and glycogen synthase kinase-3b (GSK-3b). DISC1 has been found to be important in neurodevelopment through its involvement in neurite outgrowth, neuronal proliferation and migration. However, the role of this protein in synaptic plasticity is unclear. The aim of this project is to determine whether DISC1 plays a role in synaptic plasticity and to elucidate the molecular pathways involved in this function. Using mutant DISC1 mice, L100P and Q31L, we have shown that DISC1 is involved in long-term potentiation and long-term depression at the hippocampal CA1. Biochemical analyses of these DISC1 mutants also show changes in Rac1 signaling, a well-recognized pathway for regulation of the actin cytoskeleton. We hypothesize that DISC1 plays a role in synaptic plasticity via its interaction with the guanine exchange factor, Kalirin-7, to regulate the Rac1 signaling pathway.

3-B-38 Identifying the interacting regions between the NMDA receptor complex & ND2 in the Src-NMDAR pathway.

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Upregulation of NMDA receptors (NMDARs) by the tyrosine kinase Src is critical for long-term potentiation of synaptic transmission in the hippocampus & chronic pain hypersensitivity in the spinal cord. Src is anchored in the NMDAR complex by ND2, NADH dehydrogenase subunit 2, which functions as an adaptor protein. The primary sequence requirements for the interaction between Src & ND2 have been determined, but the interacting regions between ND2 & the NMDAR complex had remained elusive until the present study. To elucidate the basis for this interaction, we transfected HEK293 cells with GFP-tagged ND2 or GFP-ND2 fragments, with NMDAR subunits or receptor controls. The NMDAR subunits/controls were fluorescently labeled, confocal images captured, & thresholded Pearson's Correlation Coefficient (PCC) was used as measure of colocalization. GFP-ND2 differentially colocalized with GluN1/GluN2A NMDARs (PPC=0.66±0.03) as compared with AMPARs (0.31±0.05), P2X4Rs (0.36±0.03), actin (0.23±0.03) or PSD95 (0.44 ±0.03) (one-way ANOVA $p<0.0001$). GFP-ND2 also differentially colocalized with GluN1 alone (0.72 ± 0.02) as compared with GluN2A (0.33±0.03). Additionally, GFP-ND2 colocalized with a GluN1-C-terminal deletion mutant (0.71 ± 0.02). The ND2 fragments 150-347 (0.74±0.05), & 200-347 (0.73±0.02) also colocalized with GluN1 alone. Thus, we have determined that GluN1, but not GluN2A, is required for colocalization with ND2, & that the GluN1 C-tail is dispensable. Furthermore, we have narrowed the requirements for the ND2 ? NMDAR complex interaction to the last 148 amino acids of ND2.

3-B-39 Using model databases to determine dendritic distributions of Ih channels in oriens-lacunosum/moleculare hippocampal interneurons

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The hippocampus is a brain region that is critically involved in memory formation and spatial navigation. Inhibitory interneurons, such as the stratum oriens-lacunosum/moleculare (O-LM) cell, are known to play dominant roles in the generation of population rhythms that are expressed during these behaviours. To better understand O-LM cell contribution to hippocampal output, we have developed multi-compartment computational models of them. However, due to the variability and incompleteness of experimental details, we are developing a database of models that collectively captures O-LM cell behaviour. In this work we aim to examine the distribution of hyperpolarization-activated cation currents (Ih) in O-LM cell dendrites, which is currently unknown We have generated an O-LM model database by varying the conductance densities of each model along physiologically plausible ranges. The resulting models were simulated within NEURON on a supercomputer cluster. The models were then ranked against electrophysiological recordings of O-LM cells using automated custom code in MATLAB. The appropriate electrophysiological characteristics to use for the ranking were determined through analysis of the experimental datasets. Our work to date indicates that models with Ih in somatodendritic regions, rather than just in the soma, are ranked more highly since they more closely conform to the experimental recordings. As such, our work suggests that dendritic Ih could directly modulate incoming synaptic input onto O-LM cells, thus affecting their contribution to hippocampal network rhythms.

3-B-40 Activation state of microglia determines neuronal survival after injury.

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Purpose: After an injury to the CNS, microglia become activated and may acquire a neuroprotective or neurotoxic phenotype depending on time course and nature of injury. Examining the effect of Lipopolysaccharides (LPS) activated microglial on neuronal survival in vivo may be confounded by the effect of LPS on other cell types. The purpose of this study is to activate HAPI microglial cell in vitro and examine the effect on retinal ganglion cell (RGC) survival when they are injected into an animal after optic nerve injury. Methods: HAPI cells were labelled in vitro with Wheat Germ Agglutinin and activated using 1 µg/mL of LPS for 24h. HAPI cells were then injected into the vitreous chamber of the rat eye (30,000 cells) or tail vein (TV; 5 x 106 cells). Retinas were examined 4-14 days following optic nerve crush (ONC) and RGC survival was determined by counting Brn3b labelled cells. Results: RGC density mirrored controls when LPS activated HAPI cells were injected into the TV with ONC for 4 days. However, after 14 days the RGC density was 51% lower than ONC alone. Following vitreous injection, there was a RGC loss of 41% without ONC and after ONC there was 53 % relative to ONC alone. Conclusion: Activated HAPI cells were neuroprotective early after injury when injected into the TV with ONC, however, they were neurotoxic later in injury. Injection into the vitreous resulted in inflammation and greater RGC death. This study demonstrates that the proximity of microglia to the injury and time course of activation determines if they acquire a neuroprotective or cytotoxic phenotype.

3-B-41 Subunit Specific Modulation of NMDAR Trafficking by Glycine in Central Neurons

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NMDARs are present at excitatory synapses and are composed of tetramers of GluN1 and GluN2 subunits (primarily GluN2A and GluN2B in hippocampus). These receptors are gated by the

coincident binding of two agonists: glutamate and glycine. During neuronal ischemia, extracellular concentrations of these agonists rise dramatically, leading to sustained NMDAR activation and excitotoxicity. As NMDAR-dependent excitotoxicity is suggested to depend on subunit composition and subcellular localization of receptors, we sought to determine how the trafficking of distinct NMDAR subtypes is altered by sustained NMDAR activation. A treatment with a high concentration of glycine alone transiently depressed evoked NMDAR-mediated currents from CA1 pyramidal neurons. To identify potential subunit-specific rules of this behaviour, we developed a live-cell imaging assay to quantify surface NMDARs expressing phluorin-tagged NMDAR subunits. With this approach, we observed that glycine induced a preferential internalization of GluN2A-containing NMDARs. Intriguingly, evidence from both imaging and electrophysiological experiments suggests that the high glycine treatment induced a transient internalization of synaptic receptors, but a persistent internalization of extrasynaptic NMDARs. At present, it is unclear whether these trafficking behaviours represent natural neuroprotective strategies employed by neurons or rather whether they contribute to toxicity. The development of a mechanistic and molecular framework of these cellular phenomena will allow us to distinguish between these possibilities.

3-B-42 Dynamic control of pannexin 1 expression by external stimuli

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Pannexin 1 (Panx1) is a large pore ion and metabolite permeable channel making major headlines in the field of cellular and molecular stroke research. According to current models, Panx1 regulates the vulnerability of neurons in ischemia, in part through mediating the dysregulation of ion fluxes. Panx1 has also been closely linked to the inflammatory responses in the brain that contribute to expansion of injury and the recruitment of phagocytic cells. In addition to previously reported expression in mature neurons and astrocytes, a recent study from our lab revealed that Panx1 is highly expressed in immature neurons. Here we provide in vitro evidence that Panx1 levels are dynamically regulated by exposure to stimuli found in the post-stroke brain, such as elevated extracellular potassium and elevated intracellular calcium. As expected, we also observe, in vivo, a robust increase in Panx1 expression in the ipsilateral ventricular zone as well as in cells surrounding the infarct, many of which are positive for markers of immature neurons. Together our data raise the possibility that Panx1 could play an additional role in regulating immature neuron survival following stroke and thereby influence the success of endogenous regenerative efforts.

3-B-43 Downregulation of brain cellular prion protein (PrPc) in insulin resistance/prediabetes: Possible implication in increased prevalence of stroke in diabetics

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Diabetes contributes to deaths of 41,500 Canadians each year and most of these (80%) will succumb to heart disease or stroke. Stroke, particularly ischemic stroke, is the leading cause of disability and the second most frequent cause of death in Canada and worldwide. The risk of stroke is increased 1.5 to 3-times in diabetic patients. Compared with control chow fed animals, Rats fed with a high fructose diet for 8 weeks exhibited a significant decrease in cortical PIP3 levels (increased PIP2 levels), as well as an elevation in both protein and mRNA levels of the protein tyrosine phosphatase (PTP1B) indicating the induction of brain insulin resistance. We also observed that both mRNA and protein expression of the cellular prion protein (PrPc) were significantly decreased in the brains of fructose fed rats compared to control chow-fed rats. Considering a neuroprotective role for PrPc, this phenomenon

may contribute to the severity and poor prognosis of ischemic stroke in diabetes.

3-B-44 Protein expression disturbances in the olfactory nervous system of smooth muscle alpha actin null mice

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Olfactory ensheathing cell's (OEC) regenerative role in the olfactory system and spinal cord injury models has been extensively studied. However, the cellular mechanisms through which this glial population perform their ensheathing functions is not well understood. Our lab's preliminary results have suggested that the absence of the prominent contractile protein smooth muscle alpha actin (SMAA) conferred abnormalities in cytoplasmic processes and nuclei of OECs. In the current study, we analyzed the protein changes in the olfactory epithelium of SMAA null mutant mice using 2-dimensional gel electrophoresis coupled with MALDI-TOF mass spectrometry. We discovered that the loss of SMAA triggered changes in the levels of various proteins that may adversely affect the cellular structural integrity. This implicates a disturbance in the regulation of protein expression in the development of OEC defects in SMAA null mutant mice. The proteins discovered provide targets for future research into the crucial protein machinery required for OEC's ensheathing function in the olfactory epithelium that can help explain its ability to facilitate regeneration of various populations of neurons.

3-B-45 Upregulation Of GluN1 and GluN2A Subunit Containing NMDARs Following Activation Of σ-1Rs In Rat Hippocampal Neurons

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Sigma-1 receptors (σ-1Rs) are endoplasmic reticulum resident chaperone proteins, and are targets for several clinically prescribed antipsychotics. It is believed that σ-1Rs exert their effects via modulation of ion channels, in particular, the glutamate gated N-methyl-D-aspartate receptor (NMDAR). However, the mechanism by which this occurs is poorly understood. Here, we show that 90 min after intraperitoneal injection of the σ-1R agonists ( )-SKF 10,047 (SKF; 2mg/kg) or ( )-Pentazocine (PTZ; 2mg/kg), a robust increase in expression of the GluN1, GluN2A and GluN2B subunits of NMDARs in hippocampal synaptosomal fractions is observed. This was abolished following a 2-day pretreatment with the σ-1R antagonist BD1047 via minipump. The expression level of the AMPAR subunit GluA1 was unaffected by σ-1R activation. Subsequent co-immunoprecipitation and surface biotinylation experiments demonstrate that the interaction between σ-1Rs and GluN2A (but not GluN2B) is significantly enhanced, and expression of only GluN1 and GluN2A subunits on the cell surface are significantly elevated following SKF injection. Electrophysiological experiments performed on HEK293 cells show that the SKF-mediated upregulation of GluN1/GluN2A NMDARs is dependent upon the presence of PSD95. As NMDARs containing GluN2A are critical for synaptic transmission at hippocampal synapses, upregulation of these receptors following σ-1R activation may underpin the effectiveness of antipsychotic drugs that ameliorate neurological disorders resulting from NMDAR hypofunction, such as schizophrenia.

3-B-46 Persistent upregulation of GABAA receptors by isoflurane and etomidate

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Many patients assume that cognitive function rapidly returns to baseline after general anesthesia, but we showed that commonly used anesthetics, isoflurane (ISO) and etomidate (ETM) causes memory deficits for at least 24 hours in wild-type (WT) mice post-anesthesia. γ-aminobutyric acid type A receptors (GABAARs) that contain α5subunit

(α5GABAARs) might contribute to such memory deficits, since pharmacological inhibition of α5GABAARs prevents these deficits. Hence, we postulate that α5GABAARs might be persistently up-regulated long after general anesthesia. To test this, mice were treated with either an inhaled anesthetic ISO or an intravenous anesthetic ETM, and 24 hours later, hippocampal tissue was obtained. Surface protein expression and mRNA levels were probed for GABAAR subunits with biotinylation followed by western blot and quantitative RT-PCR, respectively. The surface expression of β2/3 subunits, which partner with α5 subunit, increased 24 hours after ISO and ETM treatment. The surface expression of α5 subunit also increased 24 hours after ISO treatment. However, mRNA levels of the α5 subunit remained unchanged after ISO and ETM. Thus, ISO and ETM cause an up-regulation in the expression of GABAARs, that persists long after the anesthetics have been eliminated, which might not result from increases in translation. In the future we will examine whether: (1) surface expression of α5 subunit increases 24 hours after ETM treatment, and (2) the persistent increase in α5GABAARs results from increase in exocytosis or decrease in endocytosis.

C – Disorders of the Nervous System

3-C-47 Emotional and cognitive behaviour changes associated with early stages of experimental allergic encephalomyelitis (EAE), a mouse model of multiple sclerosis

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Multiple sclerosis (MS) is often associated with co-morbid neuropsychiatric and cognitive impairments, affecting around 50% of MS patients. Herein, we investigated these abnormalities in an animal model of MS, called EAE, during the presymptomatic stage of the disease. EAE was induced by immunization with MOG35-55 and the mice exhibited no motor deficits until d9 after immunization. This enabled us to carry out a series of neurobehavioral tests between d6-d8 post-immunization. EAE mice spent more time in the outer zone in open field test and in the closed arms of elevated plus maze, and showed decreased latency for immobility in tail suspension test and forced swim test compared with controls, which were indicative of anxiety- and depression- like behavior. EAE mice spent less time in the target quadrant compared to sham controls during probe trial in Morris water maze while in fear conditioning test, it displayed a trend towards faster memory extinction, indicative of memory impairment. No demyelination, microglial activation or astrogliosis was observed in the brain at this stage. Transcript analysis by RT-PCR from the brain revealed elevated IL-1β in the hypothalamus of EAE mice. Levels of IL-5 increased and MIP-2 decreased in the plasma of EAE mice, indicative of imbalance between pro- and anti-inflammatory phenotype. Lastly, plasma corticosterone levels increased in EAE mice compared to naïve. In conclusion, emotional and cognitive deficits are observed in EAE (and possibly MS) on the absence of demyelination and was associated with inflammatory and HPA axis changes.

3-C-48 Resting-state functional connectivity abnormalities in pediatric-onset multiple sclerosis: Relation to lesion volume, thalamic volume and cognitive performance

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The aim of the current study was to examine resting-state functional connectivity in pediatric-onset multiple sclerosis (MS). Methods: Eighteen

individuals aged 13-25 with pediatric-onset (diagnosis prior to age 18) relapsing-remitting MS (mean age=19, 12 female) and 18 age and sex matched healthy controls were enrolled. All subjects underwent a 45-minute neuropsychological evaluation and a 3.0 Tesla MRI scan which included a 6-minute resting-state functional MRI (fMRI) acquisition. Results: Using the posterior cingulate cortex (PCC) as a seed region, the pediatric MS group showed multiple areas of enhanced and reduced functional connectivity compared to healthy controls. Total lesion volume was correlated with functional connectivity of the PCC and right inferior parietal (r=0.76) and left superior frontal (r=-0.77) regions. Thalamic volume was positive correlated with functional connectivity of the PCC and bilateral middle frontal, right superior temporal, left superior parietal, and right superior frontal regions (all r>0.7). In the MS group, increased functional connectivity between the PCC and bilateral superior temporal regions were associated with better performance on measures of attention and processing speed (p=.036). Conclusions: There is evidence for functional reorganization in pediatric MS. Increased recruitment of bilateral superior temporal regions during resting-state was associated with better cognitive performance. MS-related reduced thalamic volume emerged as a very strong structural correlate of widespread reduced resting-state functional connectivity.

3-C-49 The Small Conductance Calcium-Activated Potassium (SK) Channel Mediate The Antidepressant-Like Effects Of Apamin And Scopolamine

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The muscarinic antagonist scopolamine (SCP) and the SK blocker apamin elicit antidepressant activity in humans and/or in rodent models. The mechanisms for these are not fully understood. Thus, we tested the antidepressant activity of SCP in the chronic unpredictable stress (CUS) model, and using intra-cerebral infusions and in vivo electrophysiology. Because M1 receptors induce calcium release from IP3-sensitive intracellular stores, activating SK conductance (Gulledge & Stuart, J Neurosci 2005), we examined whether enhancing SK activity could block SCP and apamin's behavioural/electrophysiological effects. Rats were exposed to CUS for at least 5 weeks, and sucrose preference (SP) measured weekly. CUS animals showed progressive decreases in SP, which was reversed by SCP as measured 15-24h after i.v. injection. SCP maintained normal SP levels for 2 non-drug days. Treatment of SCP with the SK agonist 1-EBIO prevented this effect. Local SCP or apamin infusion into the medial prefrontal cortex (mPFC) rapidly reversed CUS-induced decreases in SP and in active coping in the forced swim test (FST). Intra-parietal SCP had no effect on SP and in the FST. Intra-hippocampal SCP increased anxiety in the elevated plus maze. Extracellular recordings showed that acute i.v. SCP administration slightly but significantly enhanced mPFC pyramidal firing. Together, these suggest that the antidepressant activity of SCP and apamin could be mediated by mPFC pyramidal modulation evoked by a decrease in SK activity. The molecular characterization of SCP and apamin's behavioural effects is under way

3-C-50 A cell-permeating caltubin peptide enhances neuronal outgrowth to promote in vivo recovery from nerve injury in a mouse model

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Neurite outgrowth is one of the essential properties of neurons during development or regeneration following nerve injury. Recently, our lab has identified a novel protein named caltubin that is endogenous to Lymnaea stagnalis (pond snail) and is required for both central neuron outgrowth and regeneration in that species (Nejatbakhsh et al., 2011 JNs). Expressing this protein in mammalian central neurons causes enhanced neurite outgrowth and reduces retraction following injury. It binds to neuronal tubulin in both Lymnaea and

mice, suggesting that it affects outgrowth by modulating microtubule assembly. To establish the utility of this protein as a neuroregenerative tool, a fusion protein was synthesized consisting of caltubin affixed to an arginine-rich cell transduction domain for cell permeability. When applied to neuronal culture, this peptide enhanced neurite outgrowth of both murine primary cortical neurons and a human cortical cell line relative to the control groups. To determine whether this peptide enhances regenerative ability in vivo, mice underwent sciatic nerve crush and regeneration was evaluated using walking track and compound muscle action potential (CMAP) analysis. Preliminary data showed that mice treated with caltubin peptide tended to show earlier recovery than mice treated with vehicle alone. Taken together, caltubin peptide may serve as a tool for the enhancement of intrinsic outgrowth ability of neurons.

3-C-51 Identification of Pharmacological Chaperones of the Dopamine Transporter

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The dopamine transporter (DAT) is an essential regulator of dopamine signaling through its control of extracellular dopamine and its role in dopamine recycling. Hereditary dopamine transporter deficiency syndrome is a recently discovered rare pediatric condition that is caused by loss-of-function mutations in the DAT(1). The disorder is characterized by parkinsonism-dystonia and increased dopamine metabolites in cerebrospinal fluid. When expressed in vitro, the DAT missense mutations result in a reduction or absence of dopamine uptake as well as absence of mature DAT protein (1). We propose that the mutations result in ER retention of an otherwise potentially functional DAT, which could be rescued by using pharmacological chaperones. Pharmacological chaperones are molecules that selectively bind proteins in the endoplasmic reticulum and increase their folding efficiency, thereby increasing the amount of functionally available protein (2). We tested a number of compounds and have identified pharmacological chaperones that can promote maturation of both wild type and mutant DAT in vitro. Subsequently, we examined the effect of one of our pharmacological chaperones in vivo, and our data show that chronic treatment can increase striatal DAT protein in mice. Pharmacological chaperones of DAT could be used as a potential treatment to rescue DAT function in children suffering from dopamine transporter deficiency syndrome. 1.Kurian, M.A. et al. (2011) The Lancet Neurology, 10(1), 54-62. 2. Morello, J. P et al. (2000) Trends in Pharmacological Sciences, 21(12), 466-469.

3-C-52 Up-regulation of Mitochondrial Proteins in Mice Over-expressing the Dopamine Transporter

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Dopamine transporter transgenic mice (DAT-Tg) are mice with an over-expression of the dopamine transporter corresponding to a 2-fold increase in protein levels. These animals have a 40% reduction in extracellular dopamine (DA), and are classified as a genetic model of hypodopaminergia. The aim of this study is to identify postsynaptic protein changes in the striatum in response to reduced DA transmission. Postsynaptic density of DAT-Tg and WT animals was isolated and 2D-difference gel electrophoresis (2D-DIGE) to separate proteins by isoelectric focusing followed by SDS-PAGE was conducted. Analytical gels were conducted and 58 protein spots were obtained ($n=3$; $p<0.05$; fold-change ± 1.5). All proteins obtained in the 2D-DIGE were up-regulated in DAT-Tg. Fifty protein spots, identified by mass spectrometry, were found to be mitochondrial related proteins from Complex I, III, and IV of the electron transport chain. Three candidate proteins identified were chosen for verification using a classical western blot approach (NDUFS2 & NDUFS8 [Complex I], and UQCRC [Complex III]). Immunoblot studies verified up-regulation of all three proteins in DAT-Tg animals.

Total NDUFS2 was up-regulated by 35% (n=6; p<0.0001), NDUFS8 by 225% (n=3; p<0.05), and UQCRC2 by 152% (n=3; p<0.01). Preliminary experiments indicate that mitochondrial number is not increased in DAT-tg animals (WT=54.6 relative units, Tg=60.0 relative units; n=6). From initial observations, Complex I and III of the electron transport chain in DAT-Tg animals may be dysfunctional.

3-C-53 The role of STIM proteins in ER stress mediated pannexin activation

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Many neurodegenerative diseases, including Alzheimer's, Huntington's and Parkinson's Disease, are associated with an accumulation of misfolded proteins which disrupts ER function and induces ER stress. Upon activation, ER stress initiates a cascade of events leading to increased Ca2 influx and apoptotic cell death. The Ca2 -permeable pannexin family of plasma membrane channels, previously implicated in changes in plasma membrane permeability during apoptosis, is a candidate for mediating Ca2 entry during ER stress. The objective of this study was to determine if pannexin channels are activated during ER stress. Whole-cell patch-clamp recordings were performed on cultured hippocampal neurons and ER stress was induced experimentally by depleting ER Ca2 stores with thapsigargin treatment (SERCA pump inhibitor). Our results demonstrate pannexin activation in response to acute thapsigargin treatment based on pharmacological inhibition of the evoked current by pannexin blockers. Moreover, we have identified a specific ER-resident protein, the stromal interaction molecule (STIM), as a key signaling component promoting pannexin activation during ER stress. This was confirmed by the lack of pannexin current in the absence of STIM expression in pannexin 1 transfected HEK293 cells. In conclusion, our evidence proposes STIM-dependent coupling of ER stress to pannexin channel activation as a novel pathway contributing to neuronal toxicity seen in various neurodegenerative diseases.

3-C-54 The Role Of The Basolateral Amygdala In Cue-Induced Renewal Of Heroin Place Preference

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Animal studies of self-administration have shown that the basolateral amygdala (BLA) is involved in context-induced renewal of drug-seeking behaviour. Using a novel procedure based on place conditioning, we established the role of the BLA in renewal caused by a discrete contextual cue. That is, one specific aspect of the conditioning chambers (i.e., a floor tile) was manipulated during conditioning, extinction and test. Therefore, male Sprague-Dawley rats were trained to associate one compartment of a place conditioning apparatus with injections of heroin (3 mg/kg SC). This particular compartment contained the floor tile during conditioning. During extinction, the tile was removed, and it was re-introduced during the test of renewal in drug-free conditions. This experiment was performed in normal animals (n=16), and in animals implanted with bilateral cannulas aimed at the BLA (n=8). On the renewal test, normal rats displayed a significant renewal of preference for the compartment containing the floor tile. In contrast, renewal was not observed in rats infused with muscimol (0.03 nmol) baclofen (0.3 nmol) in the BLA just prior to test. These data suggest that a preference for an environment paired with heroin can be renewed after extinction by the re-introduction of a discrete stimulus that was part of the context during conditioning. In addition, the intracranial experiment suggests that the BLA modulates the interaction between various cues that create a conditioned context.

3-C-55 Metals in Myelin Repair

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Myelin is the insulation that surrounds many nerve processes both in the brain and spinal cord that form the central nervous system and in nerve

processes of the peripheral nervous system. Myelin is made by supporting cells that wrap around nerve cell processes, these cells are oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system. When damage occurs to myelin these cells attempt to repair but the repair is not always successful and we do not fully understand why. Understanding myelin repair is particularly relevant in demyelinating diseases such as multiple sclerosis (MS) and Guillain Barre Syndrome (GBS). MS and GBS are autoimmune demyelinating diseases of the central and peripheral nervous systems respectively. The ability of the oligodendrocytes and Schwann cells to restore lost myelin varies from patient to patient and directly impacts disability. Previous work in our lab has shown that electrical stimulation dramatically enhances remyelination in the peripheral nervous system. Fe, Cu and Zn have been shown to stabilize myelin in the central nervous system; however, little it is known about if and how these metals contribute to the peripheral nerve myelin. We are asking: are these metals involved in electrical stimulation enhanced remyelination in the peripheral nervous system? What role does each of these metals play with regard to proper remyelination? This research has the potential to elucidate the role of metals in myelin damage and repair in GBS extending to MS and other disorders of the myelin sheath.

3-C-56 Astrocyte-secreted factor thrombospondin-1 restores dendritic spine development in the Fragile X mouse model

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Fragile X syndrome (FXS) is the most common form of inherited intellectual disability characterized by cognitive impairment, attention deficit and autistic behaviours. This neurodevelopmental disorder is caused by silencing of the FMR1 gene, located on the X chromosome, which leads to the loss of FMRP (Fragile X Mental Retardation Protein) and dysregulated mRNA translation. Previously, our laboratory demonstrated that astrocytes could prevent and rescue abnormal dendrite morphology and dysregulated synapses that characterize FXS. However, the effect of FXS glial cells on the development of neurons has not been extensively studied. Thrombospondin-1 (TSP-1) is an astrocyte-secreted protein that has been highly implicated in promoting neurite outgrowth, survival, and neuronal maturation. Utilizing a FXS knockout mouse model and an astrocyte-neuron co-culture system, we aim to investigate the contributions of TSP-1 on dendritic spine development in hippocampal neurons. Here, we revealed that when FMR1-knockout (KO) neurons were grown in the presence of a wildtype (WT) astrocyte feeder layer, spine number was restored to that of their WT counterparts. Following treatment with recombinant TSP-1, spine density was also restored in KO neurons. Determination of TSP-1 levels in astrocyte-conditioned medium further showed marked reductions in secreted TSP-1 by KO astrocytes. These results identify astrocyte-secreted TSP-1 as a strong promoter of spine development and underscore the potential therapeutic use of TSP-1 to treat spine pathology in FXS and other related disorders.

3-C-57 Mutant Huntingtin mediated repression of antioxidant gene expression is rescued by a novel Nrf2 activating agent

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Mitochondrial dysfunction and elevated reactive oxygen species (ROS) are strongly implicated in various neurodegenerative disorders, including Huntington's disease (HD). HD is caused by an expansion of a polyglutamine repeat within the amino-terminus of the Huntingtin (Htt) protein; an event associated with oxidative stress and neurotoxicity. We previously demonstrated that overexpression of mutant Htt (mHtt) in PC12 cells leads to elevated ROS production and a concomitant decrease in expression of the antioxidant protein peroxiredoxin1 (Prx1). Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor responsible for regulating

antioxidant gene expression under the control of the antioxidant response element, including Prx1. Here we demonstrate that mHtt prevented Nrf2 nuclear translocation and activation of antioxidant enzyme expression in PC12 cells. Interestingly, treatment with the compound dimercaptopropanol (DMP) prevented mHtt-mediated inhibition of antioxidant gene expression and neurotoxicity. Furthermore, DMP exposure decreased the association of Nrf2 with Kelch-Like ECH-associated Protein 1 (Keap1), a protein which facilitates the ubiquitination and subsequent proteolysis of Nrf2. We also determined that DMP promoted the degradation of Keap1, possibly via an autophagic/lysosomal process. The identification of DMP as a neuroprotective agent that facilitates the degradation of Keap1 and promotes Nrf2 activation is highly novel. This study suggests that DMP may have relevance for the treatment of HD and other neurodegenerative disorders.

3-C-58 Role of the noradrenergic locus coeruleus complex in relapse to heroin seeking

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It is thought that relapse to drug taking involves new learning characterized by memory consolidation. These experiments were designed to explore the role of the noradrenergic (NA) cell groups of the locus coeruleus (LC) complex in the memory consolidation process engaged by relapse. To this end, we used the reacquisition model of relapse in male Sprague-Dawley rats involving: habituation, place conditioning (1 mg/kg heroin and vehicle SC; 4 pairings each over 8 days), a test of conditioning (Test I), extinction (vehicle and vehicle; 4 pairings each over 8 days), a test of extinction (Test II), reconditioning (1 mg/kg heroin and vehicle SC; single pairing each over 2 days) and test of reconditioning (Test III). Rats received bilateral intra-LC infusions of clonidine (aCSF, 4.5 and 18), an alpha2-adrenoreceptor agonist, following heroin reconditioning. To verify that intra-LC clonidine reduced central NA activity, c-fos expression was assessed in LC projection sites (i.e. basolateral and central amygdala; BLA and CeA). It was found that 18 nmol clonidine blocked heroin reacquisition when infused immediately after reconditioning, but had no effect when administered before the test of reconditioning. The same dose of clonidine infused into the LC reduced c-fos activity in the BLA and CeA. These data strongly suggest that relapse involves a memory consolidation process sensitive to manipulations of central NA activity.

3-C-59 Copy Number of the General Transcription Factor (Gtf2i) Determines Neuronal Maturation in Williams-Beuren Syndrome Model

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Williams-Beuren syndrome (WBS) and 7q11.23 Duplication syndrome are neuro-developmental disorders caused by the deletion and duplication of 26 genes on chromosome 7 including GTF2I. The syndromes are associated with neurocognitive and behavioral features with contrasting phenotypes. Osborne's group generated mice with decreased (Gtf2iDel) or increased (Gtf2iDup) genomic copy number of Gtf2i and linked the gene copy number to separation anxiety in both mice and humans. Thus providing a useful model for understanding the molecular basis of both the 7q11.23 disorders and anxiety. TFII-I suppresses agonist-induced calcium entry (ACE) by competing with TRPC3 for binding to phospholipase C-γ, which may be associated with the cognitive defects of WBS. However, the cellular effects of TFII-I deletion and duplication have not been tested. In this study we investigated the regulatory function of TFII-I on TRPC3 channels and neuronal morphology in vitro in our mouse models. Using primary cell culture we found significant differences in total neurite length and axonal branching. Furthermore we found differential distribution of TRPC3 channels in cell bodies, neurites and growth cones, supporting the notion that TFII-I regulates the cellular localization of the TRPC3 channel. Interestingly, we show

differences in ACE. Thus, TFII-I regulated ACE may play a critical role in neuronal maturation in the cortical region. Together our results using the genetic models provide functional insight into the cellular mechanisms of the 7q11.23 syndromic disorders and perhaps anxiety disorders.

3-C-60 Regulation of adult neurogenesis by the presenilins

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Presenilins (PS1 and PS2) are essential components of the ã-secretase complex associated with familial-Alzheimer's disease (AD). In the embryo, PS maintain the neural progenitor cells (NPC) and prevent premature differentiation. Forebrain-specific PS knockout mice have also revealed the PS to be essential for neuronal survival and learning & memory in the adult brain. These findings prompted us to investigate the role of PS in context of adult hippocampal neurogenesis. We hypothesized loss of presenilin within the NPC would be associated with deregulation of NPC survival, differentiation and maturation in the subgranular zone of the dentate gyrus and may contribute to the cognitive deficits associated with AD To specifically target dividing NPC in the dentate for PS ablation, we used a retroviral approach to deliver GFP-Cre and RFP (control) to adult floxed PS1 mice that were bred on a PS2 KO background. Surprisingly, infected NPC showed no defect in survival or differentiation into immature neurons at 12dpi in the absence of PS1. By 30dpi, PS-null NPC developed into NeuN mature neurons with a complex dendritic arbor similar to wild-type NPC. Finally, removing PS from the type1 radial glia using the NestinCreERT2 inducible system showed no effects on cell survival at 12, 30 or 60 days post ablation Our unexpected findings indicate that PS function is not critical for NPC development in the adult dentate. Rather, our results suggest PS may regulate NPC through a non-autonomous mechanism that involves the mature granule cells of the adult dentate gyrus.

3-C-61 EEG changes due to the subconcussive effects of participating in a season of an impact sport

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Previous studies have used quantitative EEG (qEEG) to investigate changes in brain activity due to sports-related concussion. These studies have reported a number of changes that occur soon after the injury and generally resolve within 8-10 days. Reported changes include a reduction in the mean alpha frequency, increased theta/alpha ratio, increase in beta power, and changes in coherence in frontal and temporal regions. In separate pre-season and post-season sessions, we recorded dense array EEG of varsity football (men) and rugby (women) athletes as they rested with their eyes closed. While none of the athletes had sustained a concussion during the season, we observed reliable changes in the alpha frequency without an increase in power, and increases in both beta and gamma power when comparing post- to pre-season recordings. The changes we observe in athletes over the course of a season are qualitatively similar to some of those previously noted in studies comparing acute concussion in athletes to age-matched peers. These results suggest that an acute concussive event may not be necessary to observe qEEG changes currently considered characteristic of mild TBI. It is possible that subconcussive impacts experienced through the regular play of impact sport at a high level, may produce changes in brain activity.

3-C-62 Fibromyalgia is associated with increased mean diffusivity in areas of gray matter decrease

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Fibromyalgia (FM) is a complex chronic pain condition lacking detectable pathology. Recently, magnetic resonance imaging (MRI) has revealed

brain morphological changes in FM, such as an overall decrease in gray matter (GM) volume. Our previous study used voxel-based morphometry (VBM) to show significant GM decreases in several prefrontal areas, including middle frontal gyrus (MFG), anterior cingulate cortex (ACC), and premotor cortex in a sample of 28 female FM patients compared to 28 matched controls. In this study, we aimed to determine if mean diffusivity (MD) and GM volume were associated in areas that showed GM decreases. We used MD maps from our diffusion tensor imaging (DTI) analysis to extract MD values from areas that showed GM decreases and found significantly increased MD in MFG ($p=0.005$) and ACC ($p=0.002$) in patients compared to controls. We previously found that patients over 50 drove the GM decreases and therefore divided the sample into older (n=15, >50) and younger (n=13, <50) patients to determine how FM interacts with age to produce MD alterations. This analysis demonstrated that the older patients drove the significant group differences in MD in both ACC ($p<0.001$) and MFG ($p=0.005$). In the older population, the MD values in ACC and MFG were correlated with pain intensity ratings, fatigue, and catastrophizing. These findings suggest that decreased GM volume in older FM patients is partially caused by decreased tissue density, indexed by MD, and that decreased tissue density in ACC and MFG may contribute to affective symptoms and pain sensitivity in FM.

3-C-63 Noradrenergic deficits contribute to amyloid-induced impairment in the TgCRND8 mouse model of Alzheimer's disease

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Autosomal-dominant mutations in the amyloid precursor protein (APP) gene increase the production and/or aggregation of toxic amyloid-β (Aβ) peptides and cause early-onset Alzheimer's disease (AD). Noradrenergic cell loss is well documented in AD and has been posited to play a role in cognitive symptoms as well as disease progression. We investigated behaviour, tissue levels of catecholamines, brain-derived neurotrophic factor (BDNF) mRNA and bioenergetic homeostasis in TgCRND8 mice that express a mutant (K670N/M671L V717F) human APP transgene. We found that TgCRND8 mice develop object memory impairment and behavioural despair, as well as reductions in noradrenaline and BDNF in the hippocampus and cortex, before the appearance of Aβ plaques. Animals with more advanced Aβ pathology exhibit disruptions in energetic status, along with diminished complex I III activity in the electron transport chain. To test whether the AD-like phenotypes of TgCRND8 mice might be due to altered noradrenergic tone, pre-plaque mice were treated with dexefaroxan, an antagonist of presynaptic inhibitory α2-adrenoceptors that are highly expressed on both noradrenergic and cholinergic terminals. Effects of dexefaroxan were compared to those of rivastigmine, a cholinesterase inhibitor. Both dexefaroxan and rivastigmine improved behaviour and BDNF expression without affecting tissue Aβ load. Drugs also restored complex I III activity and increased ATP levels. Reductions in noradrenergic tone appear to underlie Aβ-induced functional impairment, BDNF deficits and energetic stress in TgCRND8 mice.

3-C-64 A Cost-Utility Analysis and Feasibility Study on Early Surgical Decompression for Traumatic Cervical Spinal Cord Injury (SCI)

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Introduction: This study compares early (¡Ü24 hours since SCI) versus later surgical decompression of spinal cord in order to determine which approach is more cost effective and to examine the potential barriers to early surgical decompression. Methods: A cost-utility analysis (CUA) was performed using data for the first year after cervical SCI. The perspective of a public health care insurer was adopted. Utilities are from the STASCIS. The reasons for delays were classified into: (a) healthcare-related ("extrinsic") and (b) patient-

related ("intrinsic") factors. Results: When considering the late decompression as the baseline strategy, the incremental cost-effectiveness ratio is US$8,523,852 per quality-adjusted life year (QALY) for patients with complete SCI and US$275,390/QALY for patients with incomplete SCI. The probabilistic analysis indicated that there is no dominant strategy. While patients who underwent early surgery had a significantly shorter time period associated with extrinsic factors than individuals who underwent later surgery, both groups were comparable regarding time related to intrinsic factors. Conclusions: Although no strategy is clearly superior to the other, early decompression of spinal cord can be more cost effective than delayed surgery in one quarter of the patients with complete SCI and one third of the patients with incomplete SCI. Our benchmarking analysis suggests that health-related factors are key determinants of the timing from SCI to spinal cord decompression. Early surgery is feasible in the vast majority of the cases.

3-C-65 Membrane depolarization is a medulloblastoma tumor suppressor

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Extensive studies of medulloblastoma (MB) genomics reveal that only a few genetic events are highly recurrent, the mutated genes do not appear to converge on well-known signalling pathways, and do not suggest targets that could be used to treat a meaningful percentage of patients. We present here a genome-wide investigation of MB DNA hypermethylation in an effort to determine the genes driving tumor pathogenesis, and reveal that genetic and epigenetic events converge on synaptic electrical activity, neuronal membrane homeostasis and glutamate signalling. We performed pharmacological (glutamate agonists) and optogenetic (0.25Hz stimulation over 18hrs, on channelrhodopsin expressing tumor slices) modulation of membrane potential to functionally assess its role in MB and found a decrease in cellular proliferation, as evidenced by the 50% reduction of BrdU incorporation in a slice model of MB. We also found increased differentiation in response to glutamate agonists (20% increase neurite length treated vs controls $p<0.03$). We also show that membrane depolarization is tumor suppressive in vivo as depolarized MB cells are unable to transplant the disease in immuncompromised mice (Kaplan Meier analysis on N=8 mice). MB cells evade differentiation in response to membrane depolarization through selection of clones with genetic or epigenetic events affecting genes involved in synaptic function. Membrane depolarization therefore represents a novel form of non-genic tumor suppressor and represents an attractive therapeutic avenue for the treatment of children with medulloblastoma.

3-C-66 Evaluation of the time course of neuronal death following endothelin-1 induced stroke in rats

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The clinical heterogeneity of stroke has led to the development of many experimental models to evaluate new therapies. Of these models, the administration of the vasoconstrictive peptide endothelin-1 (ET-1) is one of the most useful because it can be directed to any brain region and it is followed by gradual, progressive reperfusion. However, the time course of cell death following ET-1 injection has not been systematically examined. Understanding this process could lead to more effective delivery of potential therapeutic agents and avoid neuroprotection/recovery confounds in preclinical studies. Our study aims to investigate the time course of neuronal death

following ET-1 induced focal ischemia in rats. Young adult male Sprague-Dawley rats received two injections of ET-1 (2µl, 400 pmol/µl) into the forelimb motor cortex. Brains were removed at the following times after stroke: 24 hr, 48 hr, 72 hr, and 7 days. We performed haematoxylin and eosin staining (H&E) to assess infarct volume and cellular morphology at each timepoint. According to MRI perfusion data using this model, the blood flow decreases rapidly (but not completely) after injection with gradual recovery over 7-48hr (Windle et al., 2006). Interestingly, most of the cell death occurs as early as 24 hours after ET-1. We will further analyse the cell morphology in the peri-infarct area to confirm the temporal profile of degenerating neurons using Fluoro-Jade C immunostaining. These results will allow us to refine the time window of administration of post-stroke treatments in future studies.

3-C-67 Neuregulin-1 / ErbB2 signaling regulates early axonal regeneration following peripheral nerve injury

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Purpose: Chronic denervation contributes to poor outcomes following nerve injury. Nerve grafts inserted from the side of an intact donor nerve into the side of a chronically injured nerve reverse these deleterious effects. This study examines whether Neuregulin-1 (NRG1), a potent Schwann cell mitogen, regulates axon regeneration and provides a mechanism for this protective effect. NRG1 signaling was inhibited with Trastuzumab, a monoclonal antibody blocking its receptor, ErbB2. Methods: The common peroneal nerves of 16 saline and 16 Trastuzumab treated rats were transected, repaired and allowed to heal for 2 or 4 weeks. Neurons were retrogradely labeled and counted in the ventral horn of the spinal cord using fluorescent dyes administered 1 cm distal to the repair site. Histomorphometry was used to quantify fiber diameter and myelin thickness within the regenerating nerve. Results: Significantly fewer neurons regenerated in rats treated with Trastuzumab (295 ± 19) compared with rats receiving saline (367 ± 23) at 2 weeks post repair ($p < 0.05$). No difference was observed at 4 weeks post-repair in Trastuzumab (330 ± 11) compared to saline (336 ± 8) treated rats. At 4 weeks, regenerated fiber diameter (FD) and myelin thickness (MT) did not differ between rats treated with Trastuzumab (FD=3.44±0.06 µm; MT=0.51±0.02 µm) and Saline (FD=3.35±0.06 µm; MT=0.55±0.02 µm). Conclusions: NRG1 signaling is required for the early phase of axon regeneration following acute nerve injury and repair. NRG1's regulation of the Schwann cell response to injury is currently being explored.

3-C-68 GDNF Mimetics: Preclinical Ventures in Neuroprotection

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Glial cell-line derived neurotrophic factor (GDNF) and its receptors (GDNF-R) are expressed in the developing and the adult nervous system. GDNF yields pro-survival signals by activating AKT and related pathways in cells expressing GDNF-R. GDNF and GDNF-R dysfunction have been implicated in degenerative diseases including Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis and Retinitis Pigmentosa (RP). The GDNF/GDNF-R axis is a validated target for the treatment of many conditions, and it has been applied successfully in multiple animal models. Moreover, GDNF has been used in human clinical trials. Nonetheless, its clinical development faces major obstacles inherent to proteins, such as high cost, poor delivering to the target tissue, poor stability, and poor selectivity. Our laboratory has promoted a conventional pharmacological approach by designing drug-like small molecule GDNF mimetics with agonistic activity, and high receptor selectivity. By using small, non-peptide

molecules with improved stability and relatively easy delivery, it may be possible to sustain neuronal function beyond previous achievements. We will present data from in vitro, ex vivo and in vivo studies on the development, the selectivity, the efficacy, the potency, and the mechanism of action of our novel drug-like GDNF mimetics. Our preclinical trials with these mimetics have yielded evidence of therapeutic merit. Further development or optimization of the lead compounds is likely to yield clinical candidates for treatment of progressive neurodegenerative disorders.

3-C-69 c-FOS expression in the basolateral amygdala during reacquisition of heroin seeking: modulation by noradrenaline.

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Within the context of animal models of relapse, reacquisition of contextual drug seeking has been found to require the basolateral amygdala (BLA; Rizos et al., 2005), and to be dependent on central noradrenergic (NA) activation. Because there are several NA terminals in the BLA, and reduction of central NA tone blocks reacquisition, it is possible that drugs that reduce central NA activity may in turn modulate cellular activity within the BLA. The present study examined c-FOS expression in the BLA induced by reacquisition of heroin place preference and modulation of this expression by clonidine (40 ug/kg; a NA alpha-2 receptor agonist). Therefore, male Sprague-Dawley rats were tested on a reconditioning protocol involving: place conditioning (1 mg/kg subcutaneous (SC) heroin and vehicle, x 4), test of conditioning, extinction (vehicle and vehicle SC, x 4), test of extinction, and reconditioning (1 mg/kg heroin and vehicle SC, x 1) followed by SC administration of vehicle or clonidine. Rats were sacrificed 90 min post reconditioning and brain tissue was stained for Fos immunoreactivity. It was found that reacquisition was associated with significantly higher Fos expression in the BLA. Ongoing research is examining Fos expression in heroin-reconditioned rats treated with clonidine. These studies suggest that NA activity in the BLA may be critical to reacquisition of heroin contextual drug seeking; a hypothesis that will be tested by selective inhibition of NA in the BLA.

3-C-70 Neutrophils are guilty of detrimental IL-1 signaling in experimental autoimmune encephalomyelitis (EAE)?

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Mechanisms underlying multiple sclerosis (MS), an autoimmune disease characterized by the destruction of myelin, remain largely unknown. In this study, we investigate the role of interleukin (IL)-1 in the EAE model of MS. EAE was induced to mouse deficient in various components of the IL-1 system by injecting MOG35-55 in complete Freund's adjuvant and Pertussis toxin (day 0 and 2). Mice lacking IL-1β (IL1β-KO) or IL-1 receptor-1 (IL-1R1KO) either have delayed onset or failed to develop EAE compared with wild-type (WT) mice. No differences were observed in IL1α-KO mice. Bone-marrow chimeric mice without these components (e.g. IL1α-KO→WT, IL1β-KO→WT, ASC-KO→WT, WT→WT, and vice-versa) revealed that IL-1β from radiosensitive cells via an ASC inflammasome are required for the induction and progression of EAE. Immunoblot showed that IL-1β, caspase-1 and ASC are transiently express during EAE in blood leukocytes (7d), then inguinal lymph node (10d) and spleen (10 & 14d) before they enter the spinal cord. The fate of lymphoid and myeloid cells of WT and IL1β-KO mice was compared in these tissues by flow cytometry, and we found that neutrophils (CD45 CD11b Ly6CINTLy6GHI) correlate with IL-1β. EAE was induced in pIL1β-DsRed transgenic mice (DsRed protein controlled by IL-1β-promoter) and we found that neutrophils in the spinal cord are mainly DsRed at the peak of EAE. These results suggest that IL-1β is critical for neutrophil recruitment in lymphoid organs and CNS

inflammation during EAE. Work to determine if targeting IL-1β in neutrophils is a good avenue against MS is underway.

3-C-71 Blood-nerve barrier breakdown in a model of neuropathic pain: Characterization and functional significance

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The blood-nerve barrier (BNB) protects the endoneurial space of the peripheral nerves from particularly harmful plasma constituents. However, in many neuropathies, breakdown of the BNB occurs. In this study we characterized and examined the functional significance of BNB breakdown in the partial sciatic nerve ligation (PSNL) model of neuropathic pain. PSNL led to a persistent BNB disruption, occurring distal to the lesion site, and lasting up to at least 4 weeks after injury. The timing of BNB breakdown was concurrent with the expression of cytokines IL-1β, IL-6, and TNFα; as well as a large influx of macrophages into the nerves. In addition, macrophages expressed vascular endothelial growth factor shortly after PSNL. The close temporal relationship of events implies an important role of local inflammatory cues in modulating BNB permeability. Also detected were changes in the tight junction associated protein zonula occludens-1 (ZO-1) expression (loss in some endoneurial vessels) and organization (disorganization at the perineurium), providing a mechanism for the molecular events that underlie blood nerve barrier breakdown. Intraneural injection of serum collected from mice with PSNL injury resulted in a decrease in mechanical paw withdrawal threshold in healthy mice, which suggested that constituents in the blood of neuropathic animals can cause pain when allowed to bypass the BNB. A BNB impermeable NaV1.7 sodium channel blocker was injected intravenously to PSNL mice to determine whether the breakdown of the BNB could be exploited for therapeutic purposes.

3-C-72 Appetitively motivated forced use of the impaired forelimb facilitates neurological recovery after focal cerebral ischemia in the rat

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Forcing use of the impaired arm following stroke promotes functional recovery in the clinic, but animal models of forced use rehabilitation have yielded mixed results. Our aim was to use a refined endothelin-1 (ET-1) rat model of focal ischemia that results in upper extremity impairments and reproducible lesions to determine if an appetitively-motivated form of forced use rehabilitation would accelerate motor recovery. Male Sprague Dawley rats (N = 23) were subjected to focal stroke via intracerebral microinjections of endothelin-1 (ET-1) to forelimb motor regions (or sham surgery). Three days later, stroke animals were then assigned to daily voluntary rehabilitation or control therapy. Rehabilitation consisted of 30 minutes of movement (exercise ball) sessions, followed by 20 minutes of task-specific exercises (pellet retrieval). A number of behavioural tests were used to assess forelimb function and determine the effect of rehabilitation on recovery. Histological and immunohistochemical examinations were performed to assess lesion volume and expression of markers of neuroplasticity. Appetitive forced use of the impaired forelimb resulted in accelerated functional recovery without exacerbating damage, and caused a shift in the cellular origin of growth factor BDNF expression. Our results suggest that improved appetitively-motivated forced forelimb use protocols may prove useful for developing new strategies to improve rehabilitation and for performing mechanistic studies of functional neuroplasticity. Supported by Atlantic Innovation Fund, Innovation PEI, and Neurodyn Inc

3-C-73 SIRT3 in Parkinson's disease

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Parkinson's disease is a neurodegenerative disorder. Symptoms of Parkinson's disease arise due to degeneration of dopaminergic neurons in the substantia nigra compacta (SNc). It is now believed that mitochondrial is central to the pathogenic process in Parkinson's disease. Sirtuin 3 (SIRT3) is a nicotinamide adenine dinucleotide (NAD+) dependent protein deacetylase which is localized in the mitochondria. Within the mitochondria, SIRT3 deacetylates substrates of the Krebs cycle and respiratory pathway to enhance ATP production. SIRT3 also regulates oxidative stress within the mitochondria. Given that the mitochondria are central to the pathology of Parkinson's disease, and that SIRT3 have many beneficial effects on mitochondrial health, we assessed the neuroprotective role of SIRT3 in cell models of Parkinson's disease. Over-expression of SIRT3 caused a 19.22±1.5% decrease in rotenone-induced cell death compared to control. We then went on to determine the mechanisms underlying the neuroprotective effects of SIRT3. We found that overexpression of SIRT3 dramatically reduced rotenone-induced depolarization of the mitochondrial membrane by 14±2% compared to control. Future studies will evaluate other potential neuroprotective mechanisms, and also determine whether SIRT3 is neuroprotective in rodent models of Parkinson's disease.

3-C-74 Effects of D-serine on visual working memory in macaque monkey.

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Pathophysiology of schizophrenia has been hypothesized to rest on the hypofunction of NMDA receptors (NR). Studies in humans and rodent models indicate that blockade of NR induces schizophrenia-like symptoms and these symptoms can be alleviated using NR co-agonists such as D-Serine (DS). We have shown that blockade of NR with ketamine induces deficits in visual working memory(WM) that are dependent on both dose and memory load in monkeys. Here we tested the effects of orally administered doses of DS(acute 1-1000 mg/kg; sub-chronic 100mg/kg/day-6 weeks) on WM ability of two female monkeys. Animals performed a sequential comparison task which required them to identify the location of a color change within an array of 2-5 colored stimuli following a retention interval (Heyselaar et al.,2011). We predicted that effect of DS on WM will be dose-dependent for acute doses and time-dependent for sub-chronic doses. We further reasoned that such effects would scale with memory load due to increased demands on WM resources at higher loads. Contrarily, we found that any of the tested doses affected neither accuracy nor latency of task responses at any memory load. We have yet to observe improvement of ketamine-induced deficits following acute DS administration. Our finding deviates from a rodent study which suggests that DS improves WM task performance (Bado et al.,2010). Failure of DS could possibly be due to saturation of NR co-agonist sites. These findings suggest that DS has limited role in affecting WM and questions its role in alleviating other cognitive symptoms of schizophrenia.

3-C-75 Inhibition of kynurenine 3-monooxygenase as a therapeutic target in the Thy1 a-synuclein mouse model of Parkinson's disease.

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Kynurenine 3-monooxygenase (KMO) is a pivotal enzyme in the kynurenine pathway of tryptophan degradation. This pathway produces neurotoxic (quinolinic acid and 3-hydroxykynurenine) and neuroprotective (kynurenic acid; KYNA) metabolites generated by KMO and kynurenine aminotransferases, respectively. Inhibition of peripheral KMO by JM6 increases KYNA in the brain. JM6 treatment in HD (R6/2) and AD (hAPP-

Tg) genetic mouse models reduces synaptic loss and microglial activation and improves behavioral deficits. These data combined with lower KYNA levels in PD patients prompted us to test the efficacy of JM6 in the Thy1 alpha-synuclein (a-Syn) over-expressing mouse model of PD. WT and Thy1 a-Syn mice were fed control food or JM6 (75 mg/kg for 1 yr). The challenging beam, adhesive removal, and open field tests were used to determine drug effects on behavioral deficits established in the Thy-1 a-Syn mice. Striatal DA levels were measured using HPLC, and real time PCR was used to determine changes in inflammatory factors. JM6 improved number of errors on the most difficult segment of the beam in Thy1 a-Syn mice, especially in trial 1 ($P<0.05$). JM6 increased the number of performers in the adhesive removal task in WT and Thy1 a-Syn mice ($P<0.01$). In the open field, JM6 normalized move episodes in the Thy1 a- Syn mice ($P<0.01$). There were no effects on striatal DA and DOPAC levels, and TNF-a and CD11 mRNA levels in the liver and spleen. Chronic treatment with JM6 improves behavioral deficits in the Thy1 a-Syn mice, supporting KMO inhibition as a novel therapeutic target in PD.

3-C-76 Molecular and behavioral analysis of APP/PS1 mice treated with Anle138b, a potential novel agent against Alzheimer's disease.

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In-vitro and cell-based studies identified Anle138b as a lead compound with protective properties. In vivo, treatment with Anle138b provided neuroprotection to DAergic neurons when tested in neurotoxin-treated or A30P mutant mice. In this study, we evaluate Anle138b as a potential therapeutic in the double transgenic APP/PS1 mouse model of Alzheimer's Disease. Anle138b was administered orally (mixed in food pellets) to wild-type and APP/PS1 mice for 4 months at a pre-plaque stage. Following treatment, mice were subjected to behavioral tests and electrophysiological analysis. In addition, we performed immunohistological analysis of plaque burden, synapse integrity and immune response activation in brain sections of Anle138b- or placebo-treated mice. We found the chronic, 4month-treatment with Anle138b to be well tolerated. APP/PS1 mice treated with Anle138b performed better than control mice in the Morris water maze during training sessions and significantly preferred the target quadrant during the trial session. The performance was identical to wt mice with the same genetic background. Electrophysiological recordings showed late-LTP of Anle138b-treated APP/PS1 mice to resemble that of wild-type control mice. Plaque deposition was reduced in Anle138b-treated mice compared to placebo-treated mice. In conclusion, Anle138b improved the cognitive performance of APP/PS1 mice and ameliorated their AD-like pathology for asymptomatic as well as symptomatic mice.

3-C-77 Increased expression of the dopamine transporter induces spontaneous degeneration of dopaminergic neurons and increased sensitivity to MPTP

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Cytosolic dopamine (DA) has been implicated in triggering oxidative stress and neurotoxicity. We propose that increasing cytosolic DA levels could heighten the vulnerability of DA neurons to insult.

The dopamine transporter (DAT) controls intracellular DA levels by taking up extracellular DA. Thus, we used transgenic mice (DAT-tg) that over-express DAT selectively in DA neurons to study the effects of enhanced DA reuptake and accumulation. DAT-tg mice were generated by bacterial artificial chromosome transgenesis. We analyzed adult (3-5 month old) mice using western blot, immunohistochemistry, HPLC, cyclic voltammetry and stereology. Mice were also treated with MPTP (15 or 30mg/kg i.p.), a Parkinson's disease (PD) inducing neurotoxin. We report increased DAT protein levels selectively in the DA cells of the DAT-tg mice. Striatal DA tissue content and release are reduced by 30% in DAT-tg mice. Notably, these mice show a 36% loss of DA neurons and a 40% increase in oxidative stress markers. When treated with MPTP, DAT-tg mice display a greater reduction in tyrosine hydroxylase immunoreactivity and DA tissue content versus wild-type mice. Our results show that even in cells that are accustomed to handling DA, increased DA reuptake can lead to neuronal loss and oxidative stress. This mishandling of DA could underlie the cell-specific vulnerability of DA neurons in PD. Since DAT-tg mice display increased neurotoxicity to MPTP and spontaneous neurodegeneration, these mice provide a useful background to study the effects of both exogenous and endogenous challenges on DA cells.

3-C-78 Selective Vulnerability of Hippocampal Sub-Fields to Oxygen-Glucose Deprivation May be a Function of Animal Age

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Purpose: The hippocampus displays regional variability in the degree of injury observed following ischemic insult. In addition, many studies have found that increasing age can worsen outcome. Given that susceptibility to injury may vary by age and region, we examined the interaction of these variables using an in vitro model of ischemia. Methods: Hippocampal slices were prepared from Sprague-Dawley rats of various ages, and challenged with 15 min of oxygen-glucose deprivation (OGD) followed by a 3 h recovery period. After this, the viability of either entire slices, or dissected sub-fields, were assessed by measuring triphenyltetrazolium chloride (TTC) metabolism. Results: Slices were prepared at 4 points across the lifespan: pre-adolescence (3 wks), late adolescence (7-8 wks), young adult (25-36 wks), and mature adult (60-63 wks). Post-OGD metabolism of TTC was similar across groups. In slices taken from animals at 15 wks of age post-OGD TTC metabolism was significantly reduced in the CA sub-fields, but not in the dentate gyrus. In contrast, when the same comparison was completed using tissue from animals at 52 wks of age, each sub-field displayed a significant reduction in TTC metabolism. Conclusions: Post-OGD TTC metabolism does not differ among slices prepared from animals between the ages of 3 wks and 14 mths. However, the reduced susceptibility of the dentate gyrus in slices from younger animals was lost in older animals. As a result, increasing age may not affect viability in general, but may alter the response to injury in specific sub-fields.

3-C-79 Fast Wallerian degeneration in Galectin-3 knockout mice

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Wallerian degeneration (WD) comprises a series of events of nerve destruction. During WD, Schwann cells and macrophages remove myelin debris, which is crucial for axon regrowth. The expression of Galectin-3 in these cells has been correlated with an efficient myelin phagocytosis, so we expected impaired axon regeneration in Gal-3-/- animals. Interestingly, we demonstrated that Gal-3-/- mice showed accelerated sciatic nerve regeneration. To clarify the underlying mechanisms related to enhanced nerve regeneration, we studied the

development of WD in Gal-3-/- mice after sciatic nerve crush. We observed that during WD, myelin breakdown and phagocytosis were increased in Gal-3-/- animals if compared to WT ones. We then explored the phagocytic ability of macrophage and Schwann cells using an in vitro-phagocytosis assay. We demonstrated that both cells from Gal-3-/- mice internalized more beads than those from WT ones. We also looked for cytokine production, since these proteins are closed related to key steps in WD, such as myelin clearance. We showed a vigorous increase in both mRNA and protein levels for IL-1β and TNF-α in Gal-3-/- injured nerves when compared to WT nerves. We also demonstrated an up-regulation in mRNA levels for TLR-2 and -4 in Gal-3-/- nerves when compared to WT nerves, 1 day after injury. Collectively, these results indicate that the lack of Galectin-3 speeds WD by augmenting the inflammatory profile of WD and by increasing the phagocytic capacity of Schwann cells and macrophages.

3-C-80 Inhibiting inflammation with CCR2/5 antagonist reverses mechanical and cold allodynia in painful diabetic neuropathy rats

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Painful diabetic neuropathy (PDN) is a common complication of diabetes which adversely affects patients' daily life. Inspired by the critical contribution of inflammation in injury models of neuropathic pain, we reasoned that if inflammation is also engaged in the pathogenesis of diabetic neuropathic pain, then 1) infiltration of immune cells in damaged nerves and/or activation of spinal microglia should coincide with the development of pain; 2) inhibiting inflammatory response in the peripheral and/or the central nervous system should reduce chronic pain. To test the hypothesis, we used behavioral and molecular/cellular approaches to explore chronic pain development and inflammatory reaction in Streptozotocin (STZ) induced diabetic rats. Our results showed that diabetic rats exhibited persistent mechanical and cold allodynia. The levels of inflammatory molecules, including cytokines, IL-1β, TNF-α; chemokines CCL2, CCL3; and chemokines receptors CCR2 and CCR5 were dramatically increased in sciatic nerves. Microglia in the spinal cord dorsal horns became activated with hypertrophic morphology and an increased cell number. Oral administration of RAP-103, a CCR2/CCR5 dual antagonist inhibited PDN associated inflammation by significantly reducing inflammatory mediators, primarily in the periphery. In coincidence, the treatment with RAP-103 resulted in a complete reversal of established hypersensitivity in STZ rats. All these results suggest that inflammation has a mechanistic role in diabetic neuropathic pain. CCR2 and CCR5 may be promising future targets for treatment.

3-C-81 Transplantation of neural stem cells in a hyaluronan-based hydrogel promotes repair following spinal cord injury

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Traumatic injury to the spinal cord causes cell death, demyelination, axonal degeneration, and cavitation resulting in functional motor and sensory loss. Stem cell therapy is a promising approach for spinal cord injury (SCI). However, this strategy is currently limited by the poor survival and uncontrolled differentiation of transplanted stem cells. In an attempt to achieve greater survival and integration with the host tissue, we examined the survival and efficacy of adult brain-derived neural stem/progenitor cells (NSPCs) injected rostral and caudal to the injury site within a hydrogel blend of hyaluronan and methyl cellulose (HAMC) into a subacute, clinically-relevant model of rat SCI. Prior to use, HAMC was covalently modified with recombinant rat platelet-derived growth factor-A (rPDGF-A) to promote oligodendrocytic differentiation. SCI rats transplanted with NSPCs in HAMC-rPDGF-A showed improved behavioral

recovery compared to rats transplanted with NSPCs in media. Rats with NSPC/HAMC-rPDGF-A transplants showed reduced cavitation, improved graft survival, increased oligodendrocytic differentiation, and sparing of perilesional host oligodendrocytes and neurons. These data suggest that HAMC-rPDGF-A is a promising vehicle for cell delivery to the injured spinal cord.

3-C-82 Effects of altered Gtf2i and Gtf2ird1 expression on the growth of neural progenitors and organization of the developing mouse cortex

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Williams Syndrome (WS) is a rare neurodevelopmental disorder caused by the deletion of 26 genes on human chromosome 7q11.23. Patients with WS show distinct clinical features including cardiovascular abnormalities, recognizable facial features, intellectual disability, disinhibition, anxiety and specific phobias, but the neurobiological bases for these symptoms remain unknown. Our lab has generated mouse models for two WS candidate genes, Gtf2i and Gtf2ird1. This study aims to determine whether change in expression of these genes affects neural stem cell physiology and neurogenesis, and subsequently contributes to the neurological features of WS. At E12.5, there is a reduction in number of neuronal precursors in mice with deletion of Gtf2i and Gtf2ird1 and an increased number of precursors in mice with Gtf2i duplication, compared to wild type littermates. βIII tubulin staining showed either no change or decreased number of neurons in the deletion mice and an increased number of neurons in the duplication mice, compared to wild type littermates. Earlier changes in neuronal development affected later stages of cortical development, where an increase in cell packing density was observed in cortical layer 4 at E18.5. These data will help us understand how the developing brain is perturbed in people with WS and may give insight into the pathological causes in WS and possibly help identify therapeutic interventions.

3-C-83 Phosphorylation and localization of huntingtin during the cell cycle

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Huntington's disease (HD) is a genetic disorder caused by a polyglutamine tract expansion in the huntingtin protein. This unstable expansion causes degeneration of cortical and striatal neurons thus emphasizing studies of post-mitotic neurons. In addition to neurological symptoms, HD is also known to affect peripheral areas of the body which makes studying the developmental aspect necessary for a thorough understanding of the disease. Huntingtin is required for proper mitotic spindle formation and orientation. Our lab has previously shown that phosphorylation of huntingtin causes localization to the centrosome and spindle microtubules, suggesting that post-translational modifications of huntingtin may play a role in the cell cycle. Our current project uses advanced biophotonic and biochemical techniques to observe the role of phosphorylated huntingtin in the cell cycle. In striatal mouse cells, different stages of mitosis were stained for phosphorylated huntingtin and we observed an increase in phosphorylation levels and differential localization of huntingtin as mitosis progressed. Through the use of SDS-PAGE, an increase in phosphorylation levels as the cell cycle progressed was observed. In the future we will repeat the previous experiments in striatal mouse cells expressing mutant huntingtin to compare the aforementioned results. Furthermore, we hope to conduct flow cytometry experiments to test the fluorescence intensity of mitotic cells. These findings can be used to target phases of the cell cycle that play a role in the developmental role of huntingtin.

3-C-84 The Neurocarta gene-phenotype database

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Understanding the genetic basis of diseases is key to the development of better diagnoses and treatments. Unfortunately, only a small fraction of the existing data linking genes to phenotypes is available through online public resources and, when available, it is scattered across multiple access tools. Neurocarta (neurocarta.chibi.ubc.ca) is a knowledgebase that consolidates information on genes and phenotypes across multiple resources and allows tracking and exploring of the associations. The system enables automatic and manual curation of evidence supporting each association, as well as user-enabled entry of their own annotations. Phenotypes are recorded using controlled vocabularies such as the Disease Ontology to facilitate computational inference and linking to external data sources. The gene-to-phenotype associations are filtered by stringent criteria to focus on the annotations most likely to be relevant. Neurocarta is constantly growing and currently holds more than 30,000 lines of evidence linking over 7000 genes to 2000 different phenotypes. Neurocarta is a one-stop shop for researchers looking for candidate genes for any disorder of interest. In Neurocarta, they can review the evidence linking genes to phenotypes and filter out the evidence they're not interested in. In addition, researchers can enter their own annotations from their experiments and analyze them in the context of existing public annotations. Neurocarta's in-depth annotation of neurodevelopmental disorders makes it a unique resource for neuroscientists working on brain development.

3-C-85 Spreading depolarization is attenuated post-stroke and may involve isoform-specific altered sodium-potassium ATPase function

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Introduction: The role of sodium-potassium ATPase (Na+/K+-ATPase) isoforms in spreading depolarization (SD) in the post-stroke brain is not well understood. Method: Mouse brain slices (350µm) (C57BL6/J, n=29) were harvested within 30 minutes following middle cerebral artery occlusion (MCAO) and incubated in ouabain (100µM or 1µM). SD was then induced by oxygen-glucose deprivation (OGD) and imaged using intrinsic optical signaling. The mRNA expression of target genes ATP1a1 and ATP1a3 (alpha1 and alpha3 isoforms of Na+/K+-ATPase) was assessed by real-time quantitative PCR (qPCR) in mice (n=6) subjected to 30-minute MCAO followed by 24 hours reperfusion. Total RNA extracted from 1mm brain slices (right and left hemispheres isolated separately) was reverse transcribed into cDNA. qPCR was performed using LightCycler 480 (Roche) and all data was analyzed using standard curve method. Results: SD onset was delayed in the post-stroke hemisphere by 33% ($p < 0.001$) and wave-front velocity was reduced by 66% ($p<0.05$). This resistance to SD was abrogated by ouabain inhibition of all Na+/K+-ATPase isoforms at 100 µM (n=16), but was unaffected by selective inhibition of the alpha2 and alpha3 isoforms at 1 µM (n=11). At 24 hours post-MCAO, ATP1a1 expression was preferentially down regulated in the post-stroke hemisphere (n=6, $p = 0.0018$), whereas ATP1a3 expression was unchanged. Conclusion: Cerebral ischemia induces resistance to SD. An alteration of the low-affinity, ischemia-susceptible alpha1 isoform of Na+/K+-ATPase may be implicated in endogenous post-stroke SD attenuation.

3-C-86 Associative encoding and functional connectivity in temporal lobe epilepsy

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Temporal lobe epilepsy (TLE) is typically associated with impairment in associative encoding due to hippocampal damage. This impairment may reflect abnormalities within brain networks that include the hippocampus. A recent resting-state study found that TLE patients showed reduced connectivity from the posterior cingulate cortex (PCC) to the ipsilateral hippocampus and increased connectivity to the contralateral hippocampus

(McCormick et al., 2013). In the present study, we had two main goals: (i) to explore whether TLE patients differ from controls in the pattern of activation during an associative encoding task; and (ii) to examine differences in whole-brain connectivity during rest using the PCC as a seed. Controls and left and right TLE patients were scanned during interleaved blocks of encoding novel face-name pairs and fixation/rest periods. Controls and both patient groups showed greater bilateral hippocampal activity during encoding versus rest. This effect was greater in controls than TLE patients. With respect to the connectivity analyses, controls and right TLE patients showed connectivity between the PCC and bilateral medial temporal lobe (MTL) regions, whereas left TLE patients showed connectivity between the PCC and left MTL regions. Connectivity was greater in controls than patients. Taken together, these results indicate functional differences between controls and TLE patients, particularly those with left TLE. Furthermore, our findings suggest that alterations in brain connectivity may underpin difficulties in associative encoding in TLE.

3-C-87 Parkinson's Disease Genes PINK1 and Parkin Modulate Stroke-Induced Cellular Damage Through a Mechanism discrete of Mitochondrial Quality Control Pathways

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Mitochondrial dysfunction and oxidative stress are two important pathologic events mediating ischemia-induced cellular death. Parkinson s disease gene PINK1 is protective against oxidative stress and mitochondrial dysfunction. It has been proposed that Pink1 is necessary for Parkin-mediated mitochondrial quality control which can enhance survival via selective mitophagy of impaired mitochondria. Here we investigate the role of PINK1 and Parkin in mitochondrial quality control and the importance of this pathway in neuronal survival after ischemia-induced neuronal damage. Methods: Cerebellar granule neurons (CGNs) were treated transiently with 50 μM glutamate and assessed for viability. Transient focal ischemia in adult mice was induced by 30 minutes of Middle Cerebral Artery Occlusion (MCAO) followed by 72 hours reperfusion. Results: We demonstrated that PINK1-deficiency sensitized CGNs to glutamate-induced excitotoxicity. Overexpression of PINK1 not only reversed this sensitivity but also was protective against excitotoxicity. Loss of PINK1 significantly increased the infarct volume in a MCAO model of ischemia. We have shown that mitochondrial targeting motif of PINK1 was not essential for its protective effect. Expression of wild type Parkin could reverse the sensitivity to cytotoxicity induced by Pink1 deficiency. Our data did not support any role for mitochondrial quality control in our ischemic stroke models. Conclusion: Our findings bring more evidence supporting the important role of these genes in cellular defence against oxidative stress and Ca2 disregulation.

3-C-88 Age-dependent time courses of recovery for motor functions following acute toluene intoxication in rats

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Toluene is a psychoactive chemical found in many household products including adhesives and thinners; inhalation of toluene vapors causes euphoria and impairments in motor control and neurological functioning. Misuse and abuse of toluene is most common in children, which may in part be due to an age-dependent neurobehavioral sensitivity to toluene. Here we assessed the effects of acute binge-like toluene inhalations (15 or 30 min; ~5000 ppm) on tasks that examine locomotion, exploration, balance, gait, and neurological functioning for adolescent (1 month), young adult (2-3 months), adult (5-6 months) and older adult (10-12 months) rats. Both motor and neurological functions were impaired following acute toluene inhalation at all ages. However, only

the duration to recover from deficits in motor functions differed among age groups, with adolescent and young adult rats requiring notably longer recovery times than older rats. Our results are suggestive of an age-dependent vulnerability to the intoxicating effects of toluene.

3-C-89 Activation of PI3K/Akt survival signaling a key to boost neural stem cell grafts in Hemiparkinsonian rats

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Transplantation of Neural Stem Cells (NSC), a powerful tool for cell replacement therapy in Parkinson's disease (PD), will become effective by enhancing their post transplantation survival. Present study is attempted to improve post transplantation survival of NSC in rat model of PD through activation of neurotrophin survival signaling which play a key role stem cell survival. Unilateral 6-OHDA lesioned PD rat model showed suppressed PI3K/Akt signaling (Akt dephosphorylation) concurrent to demise of tyrosine hydroxylase (TH) positive neurons in ipsilateral striatum. NSC were transplanted in this compromised striatum alone or along with sustained neurotrophin supervision of Olfactory Ensheathing Cells (OEC). We looked for restitution of PI3K pathway,its association with survival of transplants, rejuvenation of host dopaminergic system and neurobehavioral recovery. Transplanted rats exhibited significant recovery in PI3K signaling evident as enhanced p-Akt, p-GSK-3â, p-CREB, Bcl-2 and GDNF, higher in co-transplanted animals. This correlated well with enhance survival of transplanted NSC and higher neurobehavioral recovery. Retrograde transfer of transplant induced neurotrophic signals to nigra increased nigral TH immunoreactivity. We confirmed active Akt imparts protection by exposing NSC and OEC co-culture to 6-OHDA, which got abolished adding PI3K inhibitor LY294002. The results suggest that careful manipulation of PI3K signaling could be used towards improving post transplantation survival of NSC and linked functional restoration following neural transplantation in

3-C-90 Identification of Conserved Dopamine Neurotrophic Factor in Caenorhabditis elegans

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Parkinson's disease is a complex neurodegenerative disorder characterized by the selective and progressive degeneration of dopaminergic neurons within the substantia nigra pars compacta. Neurotrophic factors promote the survival, differentiation and maintenance of neurons and are potential therapeutics for the treatment of neurodegenerative disease. Conserved dopamine neurotrophic factor (CDNF) is a recently identified factor for dopaminergic neurons. It has been shown to be efficient in preventing the degeneration of these neurons and may play a role in the treatment of Parkinson's disease. Caenorhabditis elegans (C. elegans) is a powerful model for genetic analysis, their short lifecycle, fully sequenced genome, high genetic conservation and only 4 pairs of dopaminergic neurons makes them a valuable tool to study the neuroprotective effects of CDNF. The objective of this study was to determine if CDNF is expressed in C. elegans dopaminergic neurons. Total RNA from cultivated C. elegans was extracted using Trizol method and reversely transcribed into cDNA. This cDNA was amplified using human CDNF primers and a standard curve was generated. Using real time PCR the initial template mRNA copy number was calculated. The amplicons were sequenced in MOBIX facility, McMaster to confirm the sequence homology. This study was the first to identify CDNF mRNA expression in C. elegans and found that it shares significant homology with human CDNF, this simplistic model organism can be used to further study the effects of CDNF in neuroprotection. (This research was funded by NSERC)

3-C-91 Lack of FMRP shifts the generation of stem cells in the Fragile X mouse model

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Neural stem cells are self-renewing and multi-potent cells that give rise to neurons and glia in a controlled manner. Fragile X Mental Retardation Protein (FMRP), absent in fragile X syndrome, is developmentally regulated and is involved in governing neural stem and progenitor cells. The role of FMRP in early postnatal cell lineage development has not been studied in depth. Immunocytochemical targetting of early expression markers in neurosphere cultures after four days showed no significant difference in the percentage of cells labelled with Nestin and/or SOX2 between wild type (WT) and FMRP knockout (KO) mouse hippocampi. Interestingly, the expression patterns of Nestin and SOX2 differed significantly in neurospheres with ≤50 cells regardless of the genotype, indicating that these markers do not label the same population of cells. To distinguish between neurospheres derived from stem vs. progenitor cells, we used the Neural Colony-Forming Cell Assay, which generates neurosphere colonies. Large colonies (>2 mm) contain cells with high proliferative potential and fulfill the functional criteria of neural stem cells. We observed a trend wherein more of the neurospheres derived from KO hippocampi were larger than those from WT despite the absence of a significant difference in the total number of colonies between genotypes. This observation is novel and suggests that the lack of FMRP contributes to a shift towards generating more stem cells, and thus indicates that FMRP is linked to the control of actively dividing cells that contribute to brain development.

3-C-92 The role of gap junctional communication in hypoglycemic and glucose reperfusion seizures

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Severe brain hypoglycemia, as the result of an insulin overdose in diabetic patients, can cause serious clinical complications such as seizures and coma. However, the mechanisms of hypoglycemic seizure generation and propagation remain unclear. Moreover, preliminary studies have shown that reperfusion with normal glucose after a period of severe hypoglycemia can cause neuronal hyperexcitability that can have further damaging effects. Gap-junctional communication plays a critical role in the genesis of hypoglycemia related injury by engaging astrocytic networks in metabolic compensation under low glucose conditions. We found that mouse brain slices perfused with low-glucose (0.5 mM) artificial cerebral spinal fluid (aCSF) typically displayed one seizure-like event (SLE), after which they experienced an irreversible loss of evoked potentials within 30 minutes unless they were immediately rescued by normal glucose aCSF. When gap junction blockers were added to the hypoglycemic perfusate, the slices had several SLEs before evoked potentials were lost. We found that 100% (n=7) of the brain slices that showed SLEs during hypoglycemia also showed subsequent SLEs during glucose reperfusion if the rescue was immediate. The addition of gap junction blockers into the aCSF during glucose reperfusion resulted in the cessation of SLEs and normal evoked responses. These data suggest that blockade of gap junctional communication plays a neuroprotective role, both during hypoglycemic conditions, where it maintains evoked potentials for a longer period of time, and during glucose reperfusion

3-C-93 The GFAP.HMOX1 transgenic mouse model of schizophrenia: I. Behaviour and Neurochemistry

Wei Song[1], **Ayda Tavitian**[1], **Hillel Zukor**[1], **Shih-Hsiung Lin**[1], **Jacob Hascalovici**[1], **Adrienne Liberman**[1], **Xin-Kang Tong**[2], **Sanjeev Bhardwaj**[3], **Lalit Srivastava**[5], **Edith Hamel**[6], **Hyman Schipper**[1]
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The discovery of key molecules that act epigenetically to transduce ambient risk factors into established patterns of disease may provide new strategies for the treatment of schizophrenia and related disorders. Novel GFAP.HMOX1 transgenic mice were engineered in our lab to overexpress human heme oxygenase-1 (HO-1) selectively in astrocytes. At 48 weeks of age, after continuous HO-1 overexpression, GFAP.HMOX1 transgenic mice exhibit augmented dopamine and serotonin levels in basal ganglia; reduced D1 receptor binding in nucleus accumbens; increased tyrosine hydroxylase expression; induction of Nurr1 and Pitx3 with attendant suppression of their targeting microRNAs, 145 and 133b; impaired neurovascular coupling; attenuated prepulse inhibition (males); and hyperkinetic behavior. The GFAP.HMOX1 neurophenotype recapitulates key behavioural and neurochemical features of human schizophrenia and implicates glial HO-1 as a prime transducer of inimical (endogenous and environmental) influences on the development of monoaminergic circuitry. Containment of the glial HO-1 response to stressors at strategic points of the life cycle may provide a novel approach for the prevention or management of schizophrenia and other human neurodevelopmental disorders. (Supported by the Canadian Institutes of Health Research (to HMS)).

3-C-94 The GFAP.HMOX1 transgenic mouse model of schizophrenia: II. Neuropathology

Ayda Tavitian[1], **Wei Song**[1], **Hillel Zukor**[1], **Shih-Hsiung Lin**[1], **Jacob Hascalovici**[1], **Adrienne Liberman**[1], **Jeannie Mui**[2], **Hojatollah Vali**[2], **Carine Fillebeen**[1], **Kostas Pantopoulos**[1], **Ting-Di Wu**[3], **Jean-Luc Guerquin-Kern**[4], **Hyman Schipper**[1]
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The discovery of key molecules that act epigenetically to transduce ambient risk factors into established patterns of disease may offer new strategies for the treatment of schizophrenia and related disorders. Novel GFAP.HMOX1 transgenic mice were engineered in our lab to overexpress human heme oxygenase-1 (HO-1) selectively in astrocytes. At 48 weeks of age, after continuous HO-1 overexpression, GFAP.HMOX1 transgenic mice exhibit subcortical oxidative stress and mitochondrial damage/autophagy; altered hippocampal cytoarchitectonics; diminished neuronal reelin content (males); axodendritic pathology; enlarged lateral ventricles; 'unregulated' glial iron deposition that colocalizes to degenerate mitochondria and autophagic cytoplasmic granules; and increased neuronal alpha-synuclein expression with downregulation of its targeting microRNA-7b. The GFAP.HMOX1 neurophenotype bears many neuropathological features in common with human schizophrenia and implicates glial HO-1 as a prime transducer of diverse stressors into altered neurodevelopmental patterns characteristic of the disorder. Containment of the glial HO-1 response to stressors at strategic points of the life cycle may provide a novel approach for the prevention or management of schizophrenia and other human neurodevelopmental conditions. (Supported by the Canadian Institutes of Health Research (to HMS)).

3-C-95 Chronic in vivo two-photon imaging reveals dysfunctional vessel structure and blood flow dynamics in the diabetic brain after stroke

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Diabetics are more likely than non-diabetics to suffer a stroke in their lifetime, and their prognosis for recovery is poor. Diabetes is known to have deleterious effects on the vasculature of other organs, but little is known about how diabetes affects the brain. We hypothesized that blood flow dynamics in the diabetic brain are dysfunctional after stroke, and this contributes to poor recovery. We used two-photon imaging through a chronically implanted cranial window to track changes in blood flow dynamics before and after photothrombotic stroke (or sham procedures) in diabetic and non-diabetic mice. In non-diabetics, there was an initial

increase in flow velocity, lumen diameter, and red blood cell flux in peri-infarct cortex. By 7 days post-stroke, all measures returned to baseline levels. In the diabetic brain, the initial post-stroke response was the same. However, blood flow velocity and flux measurements did not normalize until 4 weeks after stroke. In order to probe for changes in blood-brain barrier integrity after stroke, we performed intravital injections of Evans Blue dye and confocal imaging of brain tissue. Vessel leakiness was significantly greater in the diabetic brain acutely post-stroke, but normalized by 7 days. Data from diabetic sham operates suggest that 2 months of uncontrolled hyperglycemia (in the absence of brain damage) does not have any obvious detrimental effects on the above measures. These data provide evidence that diabetes alters the brain's vascular response to stroke, which could damage or impede the rewiring of surviving neural circuits.

3-C-96 Effect of ischemic lesion size on bilateral motor cortex reorganization and functional recovery of rats.

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Following stroke, imaging studies in humans suggest that abnormal activation in the intact ipsi (IL) and contralesional (CL) motor cortical areas is associated with slower functional recovery. The neuroplasticity mechanisms causing this increased activity in areas remote to the lesion and its effect on functional recovery are poorly understood. However the extent of damage to the IL motor cortex has been suggested as the causal factor. In this study, we used a rat model of cortical ischemic stroke to investigate the effect of lesion size on the reorganization of cortical distal forelimb representation (DFR). Lesions were induced by injections of a vasoconstrictor in the caudal forelimb area (CFA), a putative M1. Impairment and recovery of the paretic limb after the lesion were evaluated using the Montoya Staircase Reaching test. Thirty-five days after the lesion, we used intracortical microstimulation techniques to document the bihemispheric motor organization of the CFA and rostral forelimb area (RFA), putative premotor. We found that rats with more extensive lesions had a significantly larger DFR both in CL and IL RFA (n=11, r^2=0.66, p<0.01), (n=9, r^2=0.52, p<0.05). Despite this, they still showed poorer functional recovery of the paretic limb (n=11, r^2=0.64, p<0.01). Consequently, more enduring behavioral impairment were present in rats with larger DFR in CL RFA (n=11, r^2=0.60, p<0.01). Our results suggest that larger lesions not only produce more persistent functional deficits, but also require more extensive bilateral reorganization of spared cortical motor areas.

3-C-97 The Effects of Tyrosine Hydroxylase Over-Expression on Dopaminergic and Noradrenergic Neurons

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[1]University of Toronto, [2]Duke University, [3]Emory University

Parkinson's disease (PD) is characterized by profound loss of dopamine (DA) and noradrenaline (NA) cells. Oxidative stress is believed to contribute to the pathology of PD, however the precise origin of oxidative stress remains poorly understood. Tyrosine hydroxylase (TH) is the rate-limiting enzyme in the production of both DA and NA, producing small amounts reactive oxygen species as by-products. TH can also contribute to an accumulation of free cytosolic DA, known to be neurotoxic. This study aims to investigative if TH itself renders DA and NA neurons particularly susceptible to degeneration. We developed a novel mouse model that over-expresses TH, and aim to examine if this results in oxidative stress and neurodegeneration. Immunohistochemistry revealed that expression of TH is constrained to neurons natively producing the enzyme. There is an increase in TH protein levels in 4-week-old TH-Tg mice compared to WT. Levels of TH were unchanged at later time points; however, this

coincided with reduced DA transporter (DAT) levels in aged TH-Tg mice. As DAT is a biomarker of DA cells, this may suggest cell loss. Supporting this interpretation is a reduction in striatal DA tissue content in TH-Tg mice relative to WT. Behavioural testing revealed evidence of both locomotor and cognitive impairment in TH-Tg mice. Therefore, preliminary results of this study revealed cellular and behavioural aberrations in transgenic mice that may be indicative of cell death; additional experiments will further investigate if dysregulation of TH can result in selective death of NA and DA cells.

3-C-98 Gabra5–/– mice exhibit autism-related deficits

Agnieszka Zurek[1]**,** **Zeenia Aga**[1], **Beverley Orser**[1]
[1]University of Toronto

Autism spectrum disorders (ASDs) are characterized by abnormal social interactions, deficits in communication and stereotypic, repetitive behaviors. Association and linkage studies suggest an association between mutations in chromosome 15 q11-13, which encodes Gabra5, and ASDs (Nurmi et al. 2003; Shao et al. 2003). Also, reduced levels of alpha5-subunit containing GABAARs (a5GABAARs) were observed in a Positron Emission Tomography study of autistic individuals (Mendez et al. 2012). Consequently, we hypothesized that a reduction in a5GABAAR expression causes autism-like behaviours. Wild-type (WT) and Gabra5–/– mice were tested in behavioural paradigms designed to detect common features of autism: 1) the social proximity assay was used to assess the number of social contacts between mice, 2) the frequency of ultrasonic vocalizations of P8 pups isolated from dams and the time required for the dam to retrieve isolated pups was used to assess communication, 3) the amount of time spent grooming in the home cage was measured to assess repetitive behaviour. Gabra5–/– mice show reduced social interactions as evidenced by fewer nose-to-nose and nose-to-head contacts. Gabra5–/– pups emitted a fewer number and a shorter duration of ultrasonic vocalizations. Gabra5–/– dams also took more time to retrieve scattered pups to the nest. Lastly, Gabra5–/– mice spent a greater percentage of time grooming in their home cage. These results demonstrate an autism-like phenotype in Gabra5–/– mice and support the hypothesis that a reduction of a5GABAAR expression promotes ASD-like behaviours.

3-C-99 Acupuncture induced changes in vagal function, blood pressure, and depressive symptom: a study of randomized, double-blind, sham-controlled trial for major depression

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We aimed to investigate the therapeutic and biological effects of acupuncture using the Press Tack Needle with 0.6 mm depth and its sham needle in this study. The study design was a randomized, double-blind, sham-controlled trial. Twelve healthy participants and thirty depressive patients were recruited to the study and randomly assigned to either active or sham acupuncture for 3 days. We applied the regimen of acupuncture for "Tobu-Oketsu" which is related to depression. Before and after the intervention, Holter electrocardiogram (ECG) recording and psychological tests were conducted to all participants. We evaluated Coefficient of variation R-R interval (CVRR), Cardiac vagal index (CVI), Cardiac sympathetic index (CSI), and Very low frequency (VLF) using Holter ECG. Each index was longitudinally compared with two-way analysis of variance (ANOVA), with time as a within-subject factor and subgroup (active or sham) as a between-subjects factor. Two-way ANOVA revealed significant time-by-subgroup interactions in Beck's depression inventory II (BDI-II) ($F_{2, 28} = 6.433$, $P = 0.017$), systolic blood pressure ($F_{2, 28} = 5.873$, $P = 0.022$), diastolic blood pressure ($F_{2, 28} = 5.344$, $P = 0.028$), CVRR ($F_{2, 28} = 19.118$, $P < 0.0001$), CVI ($F_{2, 28} = 11.680$, $P = 0.002$), and VLF ($F_{2, 28} = 15.362$, $P = 0.001$). While no significant interaction was observed in CSI ($F_{2, 28} = 3.020$, $P = 0.093$). The

intervention of acupuncture caused the improvement of blood pressure, autonomic function especially for vagal function and BDI-II score in patients with depression in the study.

D – Sensory and Motor Systems

3-D-100 Interhemispheric Connections of the Primary (M1) and Ventral Premotor (PMv) Cortex hand representations in the Macaque monkeys.

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[1]University of Montreal

The motor cortex of macaques is divided into several regions. M1, and several premotor areas (PM) play a fundamental role in the control of voluntary arm movements. To date, several studies have investigated the pattern of interhemispheric connections of M1 and PM, as well as the supplementary motor area (SMA). For PM, the most numerous connections are found in the contralateral counterpart. In contrast, studies on interhemispheric connections of M1 show that M1 receives a minor interhemispheric input from its counterpart in the contralateral hemisphere. This result contrasts not only with the pattern of PM but also with the strong interhemispheric effects reported between the M1 hand area. The goal of the present study was to investigate further the pattern of interhemispheric connections of M1 and to detail the topographic specificity of contralateral cortical inputs to M1 using intracortical micro-stimulation. Anterograde (biotinylated dextran amine) and retrograde (Fluoruby) tracers were injected in M1. To allow comparison within the same animal, retrograde tracer (Fast blue) was injected in PMv. Tracers were injected at different depths to ensure that all layers of the grey matter were labelled. We found that the most numerous connections of M1 are with SMA (48%). Connections with the contralateral hand area were much sparser (15%). This pattern contrasts sharply with the one found for PMv who shared most of its connections with its homotopic counterpart. Our results support that the pattern of interhemispheric connections in M1 is different than the one of PM.

3-D-101 Gaze-Dependence of Grasp Location and Orientation of Visually Directed Reaching

Noura Alomawi[1], **Joost Dessing**[2], **Xiaogang Yan**[1], **Douglas Crawford**[1]
[1]York University, [2]Queen's University Belfast

It is well known that reaches to remembering targets are gaze-dependent, that is, subjects tend to overshoot the target relative to gaze fixation. But providing visual feedback during the movement suppresses these errors, suggesting that they arise from hand-related transformations. All these findings, however, apply of target location information; gaze dependent effects for target orientation have so far not been studied. Such errors would influence grasp orientation. Here, we investigate the effect of gaze direction on grasp location and orientation errors and the influence of visual feedback of both the hand and target on these errors in healthy young subjects. Subjects reached toward and 'grasped' rectangular target represented on a large computer screen by thumb and index fingers. Reach target positions and fixation positions were randomized between three locations (left, centre, and right) and three target orientations (horizontally or tilted 45º clockwise/counterclockwise). Visual feedback was manipulated so that during the reach subjects continued to see the target, the hand, both, or neither. To date, seven subjects have been tested and a preliminary analysis has been done on four of these yielding the following tentative results: Grasp location and grasp orientation were significantly influenced by gaze direction. Visual feedback of the target had little influence on systematic and variable errors, but (surprisingly) hand feedback increased grasp location errors, perhaps due to the semi-pantomime nature of the grasp task.

3-D-102 Decreased Excitability of Face Primary Motor Cortex (Face-M1) Induced by Mustard Oil Application to Rat Molar Tooth Pulp is Dependent on the Functional Integrity of Face-M1 Astrocytes

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[1]University of Toronto

Dental pain is often associated with limited orofacial motor functions that are under the control of face-M1. The underlying central mechanisms are unclear. Our objectives were to determine whether: 1) application of the inflammatory irritant mustard oil (MO) to a rat tooth pulp affects face-M1 excitability manifested as an altered intracortical microstimulation (ICMS) threshold required to evoke electromyographic (EMG) activity in the anterior digastric (AD) jaw-opening muscles; 2) application of Methionine Sulfoximine (MSO), an astrocyte inhibitor, to face-M1 can influence the MO effect. Under Ketamine general anaesthesia, EMG electrodes were implanted in the AD muscles. Following craniotomy, a microelectrode was positioned in a left face-M1 site from which ICMS (35ms train, 12x0.2ms pulses, 333Hz) evoked low-threshold (≤30μA) AD EMG activity. This baseline threshold was monitored for 30min; then MO (N=8) or saline (N=8) was applied to the exposed tooth pulp and ICMS thresholds monitored every 5min for 15min. MSO (0.1mM, N=5) or saline (N=5) was then applied to the face-M1 and ICMS thresholds monitored for 120min. Within 15min of MO (but not saline) pulp application, ICMS thresholds increased significantly (46%; repeated-measures ANOVA, post-hoc Bonferroni, p=0.001). The decreased face-M1 excitability was normalised to baseline levels following MSO application to face-M1. The data suggests dental pain may be associated with decreased face-M1 excitability that is depends on the functional integrity of face-M1 astrocytes. Support: CIHR MOP4918, Rosenstadt funding

3-D-103 How does the brain know how well it knows what it knows?

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[1]York University

When two noisy but redundant estimates of a stimulus dimension are available (e.g. the position of an object observed with vision and haptics), the brain combines those estimates in proportion to their reliabilities. This combination rule creates a "statistically optimal" estimate. Here the term reliability refers to a measure of the noisiness of a sensory channel. For example, on a foggy night your visual estimate an approaching car's location is less reliable than in sunny conditions. Although reliability-weighted combination is found almost ubiquitously under experimental conditions, the underlying mechanisms used by the brain to actually assess the reliability of its own estimates are not fully understood. Most models that address this issue make the untested assumption that the internal estimate of a property (like position) must respond rapidly to fluctuations (i.e. the noise) in sensory input. In our work we employ a visual stimulus that indicates a position to the subject and has been shown previously to participate in optimal combination with haptic estimates of position. When presenting this stimulus to subjects we inconspicuously cause it to jump at varying time intervals before the subject must indicate its location. A careful investigation of subjects' response patterns indicates that once an estimate has been formed, it cannot be shifted quickly. In fact, our results are consistent with the idea that the stimulus estimate is maintained in an "attractor" state. This finding is inconsistent with current models of how optimal combination is computed by the brain.

3-D-104 Imaging membrane depolarization during spontaneous infraslow activity in mouse cortex reveals bilateral, functional connectivity and concurrent modulation of sensory-evoked response variability

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[1]University of British Columbia

Large-scale brain networks have been identified in spontaneous, infraslow (<0.1 Hz) fMRI BOLD signals in humans. However, the determinants and function of these very low frequency forms of activity are not clear. We imaged, with voltage-

sensitive dyes (VSD), a spontaneous, infraslow form of activity in urethane-anesthetized mouse cortex. Infraslow activity manifested as DC fluctuations in EEG and fluctuations in power spectrum from both EEG and cortical local field potential recordings. VSD imaging revealed infraslow fluctuations were pervasive over primary, secondary and association cortices and exhibited bilaterally synchronous activity. Using a seed-pixel based analysis, we found sensory-associated regions, such as forelimb and hindlimb somatosensory cortices as well as primary visual cortex, to be functionally connected in their activity within spontaneous, infraslow fluctuations with homotopic regions in the contralateral hemisphere. We next investigated the relationship between ongoing infraslow fluctuations and sensory- evoked activity. We found that the trial-to-trial variability of sensory-evoked responses, stimulation of forelimb, or light stimulation of the eye, positively co-varied with the phase of infraslow fluctuation. Also, light-evoked responses from ChR2-expressing mice demonstrated a similar relationship indicating that these changes in excitability may be intrinsic to the cortex. These data suggest that infraslow activity may influence coinciding sensory evoked activity or that both may reflect a similar process that affects both in parallel.

3-D-105 Cortical substrates for egocentric and allocentric encoding of remembered visual target locations for reach

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[1]York University

The location of a remembered reach target can be defined in egocentric or allocentric reference frames, but the neural mechanisms for allocentric reach representations are essentially unknown. Here we employed an event-related fMRI design to investigate the brain areas that support these two types of representation. Twelve participants reached with their right hand toward a remembered target location in complete darkness. Reach targets and additional landmarks were always presented for 2s, but at the beginning of each trial, participants were instructed to ignore the landmark and remember target location in space (Ego condition) or remember target location relative to the landmark (Allo condition). During the following delay period (12s) participants had to remember the target location in the appropriate reference frame. In a non-spatial Control condition, participants remembered and reported the color of the target. We found that during the delay period Ego and Allo conditions elicited higher response compared to the Control condition in bilateral Superior Parietal Cortex (SPC), Extrastriate Cortex (EC) and dorsal Premotor area (PMd) in the left hemisphere. Bilateral SPC and right PMd showed higher response to Ego vs. Allo, whereas Visual Cortex showed higher activation for Allo vs. Ego. Further, spatial selectivity was only observed in occipital cortex, with calcarine showing stronger contralateral activation for targets relative to the central gaze position, and EC showing stronger activation for contralateral targets relative to the allocentric cue in the Allo task.

3-D-106 Fast feedback corrections correlate with reach adaptation and properties of altered limb dynamics

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A hallmark of voluntary motor control is the ability to adjust motor patterns to novel mechanical contexts. Recent studies have highlighted feedback responses that express knowledge of voluntary behaviour, leading to the hypothesis that feedback responses should adapt when we learn new motor skills. Although studies suggest that learning affects feedback responses, the caveat is that adaptation tasks increase muscle activity during reaching. This additional muscle activity amplifies stretch responses, making it difficult to separate the effects of learning from automatic spinal processes. Here we examined adapted feedback responses using a novel paradigm where participants reached to three targets while adapting to a viscous elbow load. Target 1 required shoulder and elbow motion,

target 2 required elbow motion (training targets), and target 3 required shoulder motion (probe target). Our paradigm controlled muscle activity at the probe target, allowing us to perturb the elbow and identify key properties of adapted feedback responses. Importantly, reaching errors at the training targets correlated with changes in the long-latency response at the probe target, showing subjects that adapted more to the elbow load displayed greater modulation of stretch responses. These adapted responses scaled with the size of the elbow load and were only present for muscles that countered the load during training. Our results highlight an intimate link between the adaptation of voluntary behaviour and feedback control and suggest an important part of learning is to adjust feedback responses.

3-D-107 Fast feedback control requires a rapid update in state estimation

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Recent results emphasize that rapid feedback responses to perturbations reflect a flexible control process, whereby only errors that interfere with the task goal are corrected. This property clearly parallels the prediction of optimal feedback control models that were introduced as a model of sensorimotor control. An important feature of these controllers is that the control action is selected as a function of the state of the limb computed at each point in time rather than using delayed sensory feedback directly to calculate feedback responses. We tested this prediction by altering the urgency of motor responses and compared participants' performances with control models with and without state estimation of the limb position. Participants performed a postural task while perturbation pulses were applied on the elbow joint. They were instructed to return to the target in 600 or 300ms in separate blocks. We found that participants were able to increase the speed of corrective movements without inducing oscillations of the joint. We were not able to reproduce this feature of motor behaviour with models that do not estimate the state of the joint: feedback delays as short as ~35 ms (25th percentile of measured responses onsets) induced oscillations following an increase in feedback gains. Also, we were not able to find any controllers that were capable of stabilizing the joint within 300ms without updating the estimation of the state of the joint. These results suggest that feedback responses must be based on rapid estimates of the limb displacement following the perturbation.

3-D-108 Two-point touch discrimination and tactile sensitivity depends on the perceived length of the arm

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Two-point discrimination threshold depends on the number and size of receptive fields between touches. But what determines the size of the receptive fields? Are they anatomically fixed? Or are they related to perceived body size? To answer this question, we manipulated the perceived length of the arm using the Pinocchio illusion. The test arm was held at the wrist by the other, holding arm which was made to feel displaced by vibrating the tendons of its biceps (flex: lengthen test arm) or triceps (extend: shorten test arm). The perceived position of the holding arm was assessed by having the participant make a blind reach to grip the test arm's wrist and recording the distance between the reach and the actual wrist position. For control trials, the holding arm was vibrated on bone at the elbow. An array of five tactors, each separated by 3cm, was placed on the lateral surface of the forearm. Vibrotactile stimuli of 250 Hz were delivered and a two-point discrimination task and a tactile detection task were performed using two-interval forced choice designs. The two-point discrimination threshold for the perceptually lengthened arm was significantly increased from 5.1 ±0.4 cm with no tendon stimulation, to 5.6 ±0.3 cm. Sensitivity was correspondingly reduced. There were no significant changes in either discrimination or sensitivity when the arm was perceptually shortened. We hypothesize that two-point touch

discrimination depends on the size of central receptive fields that become larger and less sensitive when the arm is perceptually lengthened.

3-D-109 Optogenetic control of peripheral pain pathways in freely moving transgenic mice

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Peripheral nociceptors are afferent neurons activated by noxious stimuli. In order to selectively activate them, we generated a transgenic mouse line expressing light-gated channelrhodopsin-2 (ChR2) channels in the Nav1.8-positive sensory neurons. This approach led to the development of a novel non-invasive pain model in which remote activation of peripheral nociceptive pathways in freely moving animals is achieved optogenetically. Based on its colocalization with nociceptor-specific peptidergic and non-peptidergic markers and its ability to drive action potentials under blue light pulses, ChR2 was found to be functionally expressed in nociceptors. Strong expression of ChR2 translated into robust acute behavioral responses ranging from paw licking and withdrawal to escape, jumping and vocalization. Also, this mouse line provides a potential chronic pain model in which plasticity in the nociceptive circuitry can be investigated. ChR2-expressing mice were sensitized by prolonged sub- and supra-threshold blue light stimulations in awake and anaesthetized animals respectively, displaying thermal and mechanical hypersensitivity post-stimulation. Using acute spinal cord slices, we recorded light-evoked NMDAR-dependent LTP, measured by an increase in fEPSP following blue light stimulation of the afferent terminals projecting to laminae I and II of the dorsal horn. Altogether, our in vitro and in vivo findings, along with the absence of light-evoked neurogenic inflammation, suggest that pain hypersensitivity is due to central sensitization and long-term changes at the CNS level.

3-D-110 Continuous visuospatial updating in superior colliculus neurons during smooth pursuit eye movements: effect of target visibility and behavioural relevance

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Recently we found that the superior colliculus (SC) visual memory response is continuously updated during smooth pursuit (SP) eye movements in a paradigm where animals were trained to spatially update the location of a saccade target across an intervening SP. A number of labs have studied neural responses to either visual targets or targets updated across eye movements, but in real life both of these are present at the same time. Here, for the first time, we study how they interact. In this study we have used a modified version of the task where 2 targets (white and orange) were shown simultaneously. Only saccades to the white target were rewarded, so animals learned to ignore the orange target. 50% of the trials had the saccade target visible for the entire duration of the trial and rest had the target visible only during initial fixation and subjects were required to keep the location in memory and update it across SP. In total, we studied the responses of SC visual neurons (n=48) across 4 different conditions: 1) visible target corresponds to neuron's RF during SP, 2) visible distracter corresponds to neuron's RF during SP, 3) memory target corresponds to neuron's RF during SP and finally 4) memory distracter corresponds to neuron's RF during SP. These modifications in the paradigm allow direct comparison of visual and updating responses as well as if the visual and updating response depend on active attention. Preliminary results suggest that updating responses are generally weaker than visual responses and attention towards updated target leads to bigger response.

3-D-111 Ipsilateral connections of the primary motor cortex in a New World monkey.

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The primary motor cortex (M1) plays a central role in the control of movements in primates. While M1 receives inputs from several premotor cortices as well as primary somatosensory cortex (S1), it is still unclear as to how these connections contribute to the control of movements. Thus, we examined the organisation and topographic specificity of cortical inputs to M1 originating from S1, the dorsal and ventral premotor cortex (PMd and PMv) and the supplementary motor area (SMA). In this study a combination of electrophysiological and anatomical approaches were used in two naïve New World monkeys (Cebus apella). Intracortical microstimulation (ICMS) was used to define the forearm and hand area in M1, PMv, PMd and SMA. As for S1, it was delineated with recordings of multiunit neuronal activity. Based on ICMS maps, injections of neuronal tract tracers were made within the hand representation of M1 (Fast blue, Fluoro-ruby, Fluoro-emerald and Biotinylated dextran amine). Following flattening of the cortex and tangential cutting, the distribution of labelled cell-bodies was documented and paired with the electrophysiological data. With physiological borders now defined in the tissue, we observe that the rostral portion of M1 receives inputs from S1, premotor areas and areas of the prefrontal cortex. However, most of the inputs to the caudal part of M1 originate from S1. Our results indicate that regions within the hand representation of M1 have particular pattern of cortical inputs, which may allow subdivisions within M1 to play different roles for the control of hand movements.

3-D-112 Reconstructing visual stimuli using population receptive field estimates

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The population receptive field (pRF) model has been used to map the retinotopic organization of multiple visuals areas (Dumoulin & Wandell, 2008).The pRF model can be easily inverted so as to generate a prediction of the pattern of visual stimulation.We sought to develop an algorithm for generating stimulus reconstructions using trained pRF estimates and novel patterns of stimulation. Participants' brains were scanned with a 3T MRI scanner and a 32-channel head-coil. Standard retinotopic mapping procedures were performed.The pRF estimates were computed for each participant from data collected in a localizer scanning session.Followup scanning sessions included standard phase-encoding stimulation patterns including an expanding ring and a rotating hemifield.Stimulus reconstructions were generated using the pRF estimates from the localizer session and functional datasets from followup sessions.We were able to use pRF estimates to generate stimulus reconstructions for various moving visual stimuli.In addition, we were able to show that reconstructions capture the effects of visuospatial attention.Image similarity metrics indicated that visual area V1 appears to represent the sensory driven aspect of the task while areas V2 and V3 seem to encode the spatial attention aspect of the task.We have demonstrated that pRF estimates can be used to reconstruct novel moving visual stimuli from functional brain imaging data.Furthermore, voxel selection criteria for generating stimulus reconstructions can elucidate which aspects of a stimulus or task a visual area extracts and represents.

3-D-113 Investigating reference frame specificity of motion-processing cortex for the temporal summation of transsaccadic motion signals

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The visual system is required to temporally summate motion signals across eye movements to form a coherent percept of a moving object. Known

as transsaccadic perception (TSP), it has been proposed that this may take place in middle temporal (MT) cortex. We aimed to investigate whether MT is the principal neural substrate of TSP of motion by implementing a transcranial magnetic stimulation (TMS) paradigm. Participants performed a motion discrimination task with TMS (left MT or Cz), or without. Furthermore, the stimulus was presented across eye movements in either invariant spatiotopic (Condition 1) or retinotopic coordinates (Condition 2); a control condition without eye movements was also performed (Condition 3). Psychometric functions were calculated by fitting a cumulative Gaussian, with motion sensitivity (β) estimated as the inverse of the standard deviation, and bias (α) at the chance intercept. Results revealed no significant effect of site or condition on motion sensitivity. Additionally, there was no significant effect in the bias for site or condition, although there was a significant difference in bias between the control condition versus a baseline task, with a shift in the point-of-subjective stationarity (PSS). The lack of any specific TMS effect on the transsaccadic summation of either retino- or spatiotopic motion signals suggests such a mechanism might not be confined to a solitary cortical region. Possible future experiments plan to explore the visual-field specificity and temporal-dependency of global motion parameters.

3-D-114 Do dopamine neurons couple arousal and motor activity?

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Abnormalities in the dopamine (DA) system have been linked to motor disturbances during sleep. Previously, we showed that an excitatory DA drive onto motoneurons during waking is lost during sleep. Here, we seek to identify the dopaminergic circuitry involved in regulating motor activity during waking. 10 rats were sleep deprived for 6 hr and 5 rats were allowed to recover sleep for 2 hr. Double immunohistochemical staining for c-fos and tyrosine hydroxylase (TH) was performed to determine sleep/wake specificity of DA structures. To determine dopaminergic projections to the trigeminal motor pool (Mo5), we perfused Fluorogold into Mo5 of 4 rats, and immunostained for TH. To determine the effect that stimulation of A11 DA neurons has on cranial motor pool activity, we implanted 10 rats with electrodes to record electromyogram of the masseter muscles and perfused NMDA into the A11 region. In 5 of these animals, we also perfused a D1 receptor antagonist in the Mo5 prior to and during A11 stimulation. We found that A11 neurons were significantly more active during waking (64% were c-fos/TH positive). Only A11 neurons projected to the trigeminal motor pool. Moreover, direct stimulation of A11 neurons significantly increased masseteric muscle tone. This increase in activity was partially reversed by blocking D1 receptors. These results indicate that the hypothalamic DA neurons project to and activate motoneurons during waking. This waking drive is withdrawn during sleep. We conclude that this DA circuit is important for coupling arousal and motor activity.

3-D-115 Acute exogenous serotonin application does not affect adult rat V1 LTP in vivo

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Long-term potentiation (LTP) serves as a mechanism mediating changes in synaptic connectivity during development and following various types of experiences. Serotonin (5-HT) plays important roles in neurotransmission and neuromodulation throughout the CNS, including the heterosynaptic facilitation of synaptic strength in various sensory cortices, including the primary visual cortex (V1). We examined the effects of exogenous 5-HT application on the modulation of LTP in the mature, thalamocortical visual system of urethane-anesthetized rats. Theta-burst stimulation of the lateral geniculate nucleus resulted in LTP (about 28% potentiation) of field postsynaptic potentials (fPSPs) recorded in V1 in the presence of local, cortical application of artificial cerebrospinal fluid (aCSF). Surprisingly, the presence of 5-HT (0.1

and 10 mM) resulted only in minor, non-significant changes in the levels of LTP observed under these experimental conditions (37% and 33% LTP for 0.1 and 10 mM, respectively). Additional analyses of spontaneous electrocoticogram (ECoG) activity in V1 showed that the ECoG was dominated by large amplitude, lower frequency oscillations, with power concentrated at frequencies below 10 Hz. This pattern of ECoG activity was not reliably altered by the application of 5-HT at either concentration. Together, these data suggest that local application of 5-HT does not necessarily modulate LTP, or affect the spontaneous oscillations occurring in the mature V1 of rats under urethane anesthesia.

3-D-116 The effect of prolonged bedrest on the perceptual upright

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Bedrest with the head in 6° down has been used as an analog of exposure to microgravity because of the prolonged release of the normal 1g force acting along the long axis of the body. Bedrest has been a useful model to explore the effects of this release on physiological measures such as cardiovascular strain and bone growth. However, exposure to microgravity also has profound effects on perceptual systems causing periods of disorientation and nausea. Although older studies suggested that there were no effects of microgravity on basic sensory processing not involving the vestibular system, more recent studies have suggested profound changes in visual processing. We therefore investigated the effect of bedrest on visual and non-visual cues to orientation. Nine subjects were recruited by the German Space Agency and subjected to rigorous medical screening. They were then put into bedrest for two periods of 3 weeks separated by 6 months. The perceptual upright was measured using the OCHART technique in which the "most upright" orientation of a character was assessed while visual cues (provided on a shrouded laptop), gravity and body cues (manipulated by posture) were separated. Assessments of the weightings were obtained before, during and after the bedrest period. There was a reduction in the weighting assigned to vision comparable to what we had observed earlier during long term exposure to microgravity in space (J. Vest Res. (2011) 21: 72). These studies validate the use of bedrest as an analog of exposure to microgravity for neural as well as vegetative physiology.

3-D-117 Monocular deprivation alters the size of FoxP2 cells in the cat lateral geniculate nucleus

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A central characteristic of the visual system is the streaming of information through parallel pathways. In the cat lateral geniculate nucleus (LGN), parallel processing streams derive from two principal neuron types, namely X and Y cells. It is well known that disruption of visual experience by monocular deprivation has a profound impact on the structure and function of Y cells, but the extent to which deprivation influences X cells remains unclear. Recently the FoxP2 protein has been shown to selectively label X cells in the ferret LGN, providing an opportunity to examine whether X cells are modified by monocular deprivation. In this study, FoxP2 labeling was examined in the LGN of normal (n=2) and monocularly deprived (n=3) cats. We first determined that the labeling characteristics of neurons reactive for FoxP2 were consistent with it being a selective marker for X cells in the cat LGN. Monocular deprivation for either a short or long duration did not change the number of FoxP2-positive neurons between non-deprived and deprived LGN layers. However, cell measurements revealed that in deprived LGN layers, X cells were reduced in size by 20% after 7 days of deprivation, and by 30% after 7 weeks of deprivation. Our results demonstrate that labeling for FoxP2 effectively identifies X cells in the cat LGN, and also that the effects of monocular deprivation are not exclusive to Y cells. Our observation of an alteration to X cells in the context monocular deprivation is congruent with the associated impairments to vision.

3-D-118 Cortical oscillations accompanying inhibitory control: Is response withholding different from response switching?

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We conducted an MEG study to compare cortical activity associated with either complete inhibition (withholding) or with response switching, of a cued motor response to distinguish any differences in preparation, inhibition, or error processing. Subjects were required to press a button in response to a rapidly presented stream of digits, and either withhold their response for an infrequent target digit (withhold task), or switch response fingers (switch task). Response preparation was similar in both tasks, as demonstrated by similar early beta suppression in MI, followed by a rebound - the latter of which was not observed in correct withholding. Frontal theta activity, thought to reflect active inhibition of the prepotent response, was also observed for both correct switch and correct withhold trials with similar frontal midline peak locations. Increased theta activity was observed in the frontal cortex for error responses, possibly indicative of error processing, which differed between tasks in both pattern of activation, as well as in location. This activity appeared to reflect two temporal components for each task, arising from multiple prefrontal sources. These results suggest that tasks requiring a switch to an alternative, or withholding a response, involve similar preparatory activation and activate similar areas associated with inhibitory control (e.g. frontal cortex), yet involve different areas and patterns of activity for erroneous responses, possibly related to different response selection requirements.

3-D-119 The effects of 30-Hz continuous theta-burst stimulation on human primary somatosensory cortex

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The primary somatosensory cortex (SI) plays a crucial role in processing sensory information relevant to the hand and motor performance. Activity in SI may be monitored using somatosensory-evoked potentials (SEPs). Traditional 50-Hz continuous theta-burst stimulation (cTBS) over the primary somatosensory cortex (SI) leads to short-lasting suppression of SEPs in the stimulated hemisphere (1), however these findings are not consistent (2). A modified 30-Hz version of cTBS may be more effective at inducing cortical plasticity (3). The purpose of this study is to investigate changes in SEPs following cTBS over left SI hand representation. Electrical median nerve stimuli of the left and right wrists were delivered to measure changes in both hemisphere SI before and for 45 minutes following cTBS. It was hypothesized that SEPs would be suppressed for 25 minutes. This work is significant because it may support an effective approach of modulating SI activity with 30-Hz cTBS (1) Ishikawa et al. Clin Neurophysiol 2007; 118: 1033-1043. (2) Katayama et al. Clin Neurophysiol 2010; 121: 2097-2103. (3) Goldsworthy, Pitcher and Ridding. Clin Neurophysiol 2012; 123: 2256-2263.

3-D-120 Cellular stress response pathway controls thermal pain sensation via translational regulation of TRPV1 activity

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Here we report that eIF2a pathway, an integrator of cellular stress responses and an important regulator of mRNA translation, is involved in control of thermal threshold. Various noxious stimuli regulate the phosphorylation of eIF2a, and mice with decreased eIF2a phosphorylation (eIF2awt/s51a) exhibit reduced thermal pain sensation and decreased nocifencive behaviour in formalin test. Pharmacological attenuation of eIF2a

phosphorylation or deletion of eIF2a kinases - PERK, GCN2 or PKR-- similarly decreased thermal pain sensation, whereas increasing eIF2a phosphorylation had the opposite effect. This phenomenon was not observed in mice with genetic deletion of TRPV1, a major heat sensor, suggesting that TRPV1 is involved in eIF2a-mediated regulation of thermal pain thresholds. While TRPV1 protein levels were not reduced in eIF2awt/s51a mice, TRPV1 activity was decreased, presumably as a result of enhanced translation of alternative splicing variant TRPV1beta mRNA, whose protein product inhibits TRPV1 function. In summary, we found that the cellular stress response pathway controls thermal sensation via translational regulation of TRPV1 activity, a mechanism that might be utilized to alleviate pathological heat sensation.

3-D-121 Asynchronous activity and stimulus discrimination in networks of spiking neurons

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Oscillations are prevalent among many areas of the brain and play a fundamental role in neural communication and stimulus discrimination, yet the mechanisms by which temporal waves of activity contribute to information processing remain poorly understood. One possibility is that oscillations increase the synchronization (i.e. in-phase neurons - Figure 1A) of spikes across neurons, forming a useful neural code for information processing. Another possibility is that asynchronous oscillations (i.e., out-of-phase neurons, Figure 1B) enhance information processing. We employ a computational model of randomly connected leaky integrate-and-fire neurons to examine these two scenarios. The model produces chaotic and spontaneous spikes with no obvious temporal structure (Figure 1C); introducing synchronous oscillations elicits temporal structure (Figure 1D), and asynchronous oscillations produce activity similar to chaotic neural networks (Figure 1E). The network was then presented with stimuli by depolarizing a subset of neurons, and the ability of post-stimulus spikes to discriminate stimuli was assessed using an mean rank analysis. Consistent with experimental data, compared to networks with no oscillations, networks with oscillations yield higher stimulus discrimination (Figure 1C). In addition, compared to networks with synchronous oscillation, asynchronous networks show enhanced discrimination (Figure 1D). In sum, our work shows that oscillations seem to convey more information processing capability when presented asynchronously to a local network of interacting neurons.

3-D-122 The investigation of 30 Hz continuous theta-burst stimulation over the primary somatosensory cortex on tactile perception

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Temporal order judgement (TOJ) is the ability to detect the order of occurrence of two sequential stimuli. Previous research has shown that TOJ with versus without conditioning stimuli impairs TOJ performance and this phenomenon is suggested to be mediated by primary somatosensory cortex (SI) GABAergic interneurons that cause perceptual binding across the two skin sites and therefore decrease the ability to identify which stimuli was received first. Continuous theta-burst repetitive TMS (cTBS) delivered at 50 Hz alters tactile perception when applied over SI. A previous report suggests 30 Hz cTBS may induce more reliable and effective changes on cortical excitability (Goldsworthy, 2012). The purpose of this study is to examine TOJ perception before and after 30 Hz cTBS over left-hemisphere SI. TOJ was performed on the index and middle finger (digit 2 and 3) and participants were queried to report which digit received the first stimulus within the pair of sequential stimuli. Subjects participated in two separate sessions that tested TOJ without conditioning stimuli and TOJ with conditioning stimuli (a low amplitude sinusoidal vibration). CTBS

was delivered over SI on both hemispheres to evoke excitability changes within the stimulated cortex. TOJ thresholds were obtained from both hands using the Cortical Metrics Device (Holden, 2011). Psychophysical measures were recorded before cTBS and at five intervals for up to 42 minutes following stimulation. Our group hypothesizes impaired TOJ performances for up to 18 minutes following 30 Hz cTBS. (Rai, 2012).

3-D-123 Allocentric Spatial Cues Influence Memory-Guided Head Free Gaze Shifts

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It is unknown how the nervous system utilizes allocentric information (locations of objects relative to other objects) when performing memory-guided gaze shifts. To address this issue we developed a novel head free memory-guided gaze task with interleaved allocentric cueing trials. Eye and head movements were measured in monkeys using search coils. Stimuli were displayed on a screen encompassing 90x80°of the visual field. During cued trials, an allocentric cue was presented with the central fixation point and could appear proximal or distal to the flashed memory target location. On a subset of trials, the allocentric cue was surreptitiously shifted 4° to the left or right. A visual mask was presented briefly prior to the saccade in order to prevent the subject from perceiving changes in the allocentric cue location. From this task we examined how allocentric cues (presented in different spatial locations with different degrees of spatial stability) influence gaze behaviour. Results show that stable allocentric cues reduce endpoint variability and shift gaze endpoint in their direction. Shifted allocentric cues bias gaze endpoint toward the shifted direction most strongly when the allocentric cue is more eccentric than the target. These results suggest that neural networks computing visuomotor transformations code for and combine allocentric and egocentric information. A modified version of this task has been used during neural recordings in the frontal eye fields to examine how multiple stimuli influence visual response fields. Supported by CIHR, NSERC and CRC.

3-D-124 Task performance and corticomotor excitability in young and older adults during visuo-haptic and auditory-haptic tasks

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Few studies have examined the impact of normal aging on behavioural and physiological aspects of haptic sensing. Given the evidence for multi-sensory interactions in the tactile system, we hypothesized that adding multisensory stimulation in the form of visual and auditory inputs should increase haptic facilitation of the corticomotor system and enhance haptic sensing performance, particularly in seniors. Participants engaged in haptic sensing of vibration magnitude with or without congruent visual (watching their finger vs. blindfolded) and auditory stimuli (congruent frequency tone vs. white noise). Single-pulse transcranial magnetic stimulation (TMS) was used to probe the excitability of the motor cortex. Contact force profiles at the fingertip were recorded between conditions to provide a second measure of changes in central motor control. Response times and accuracy of responses were recorded to detect any changes in performance. Results: Watching the finger was distracting for all ages, decreasing discrimination accuracy and corticospinal excitability in young adults, and increasing normal force variability in older adults. Listening to the 250Hz tone was helpful to older adults, increasing discrimination accuracy. These findings indicate that motor control during haptic sensing of vibration magnitude may be influenced by visual and auditory inputs, in young and older adults, providing a physiological basis for rehabilitation specialists to develop multisensory interventions to promote recovery of haptic sensing after neurological impairments (e.g., stroke) or aging.

3-D-125 Recovery of central vestibular neuron detection thresholds following unilateral labyrinthectomy

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The vestibular system is responsible for processing self-motion, allowing normal subjects to detect rotational movements as slow as 1-2º/s. Immediately following unilateral vestibular injury patients can only detect motion as slow as ~20º/s. Here, we determined motion detection thresholds of first order central neurons which provide input for self-motion perception (vestibular-only neurons in the vestibular nuclei). In normal animals, neurons show robust responses to vestibular stimulation and have detection thresholds of 15º/s. Immediately following unilateral labyrinthectomy vestibular sensitivities dramatically decrease, but improve within 3 weeks reaching values close to normal. Accordingly, one might expect detection thresholds to increase immediately following lesion and improve over time and reach control values. Our results show that immediately following lesion, neuronal detection thresholds do increase (30º/s) and slightly improve within 3 weeks (24º/s), but do not recover to control values. Interestingly, we found the increased vestibular sensitivity was effectively offset by an increase in response variability thereby causing detection thresholds to remain higher than control over the course of recovery. Taken together, our results suggest that the mechanism that drives vestibular compensation (reweighting of sensory inputs) cause an increase in response variability, which affects the processing of vestibular information.

3-D-126 Evidence for a reference frame transformation of vestibular signal contributions to reach planning and execution

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Vestibular signals contribute to the planning and execution of voluntary reaching movements during body motion. However, to contribute appropriately they must be transformed from a head- to a body-centered reference frame. To investigate the evidence for such a transformation bipolar galvanic vestibular stimulation (GVS) was used to simulate rotation about a roughly naso-occipital head axis as human subjects reached in the horizontal plane with their head in different orientations. If vestibular signals that contribute to reaching have been transformed from a head- to body-centered reference frame, the same stimulation should be interpreted as rotation about a body-horizontal axis with the head upright and about a body-vertical axis with the head tilted forward. Thus, GVS was predicted to perturb reach trajectories in a head-orientation-dependent way. In keeping with this prediction, we found that GVS-induced trajectory perturbations were significantly larger with the head forward as compared to upright. Only with the head forward were trajectories and endpoints consistently deviated in the direction that would provide spatial compensation for rotation about a body-vertical axis. These results directly demonstrate that vestibular signals contributing to reaching have indeed been transformed from a head- to a body-centered reference frame. By comparing the effects of GVS applied during versus prior to reaching we also provide evidence that transformed vestibular signals contribute to distinct compensation mechanisms for body motion during reach planning versus execution.

3-D-127 Effects of Head Orientation on Tactile Localization

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We present a series of studies on the effect of head orientation on tactile localization. Vibration stimuli (250 Hz) was presented from an array of eight tactors attached to the front or back of the torso while participants oriented their head approximately 90° to one side. Participants

indicated the perceived location of the touch on a visual scale that represented the extent of the tactile array. Systematic localization errors were found that depended on (a) whether the tactor was on the same side of the body as the head was turned and (b) whether the head was returned to the central position before indicating the perceived location. We will discuss the possibility that (a) reflects lateralization of tactile target representation in the brain and argue that (b) indicates different reference frames used for coding touch location depending on the task. We hypothesize that an underestimated neural gaze signal affects both the perceived gaze direction and perceived body straight ahead, likely reference points used in the spatial coding of touch. Finally, we find that the perceived shifts of tactile stimuli on the body do not rotate around the front and back of the body, but that the shifts on the front and back are mirrored. This may indicate that the body representation used to locate touches in external space represents "front" and "back" space in separate parallel representations, rather than as three-dimensional whole.

3-D-128 Decreased Excitability of Rat Face Primary Motor Cortex (Face-M1) Induced by Noxious Tooth Pulp Stimulation is Modulated by Trigeminal Brainstem Astrocytes

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Dental pain may disrupt orofacial sensorimotor functions, and is associated with an increased excitability of trigeminal brainstem sensory nuclear complex (VBSNC) neurons that is dependent on VBSNC astrocyte function. We examined if application of the inflammatory irritant mustard oil (MO) to a rat tooth pulp affects face-M1 excitability defined by intracortical microstimulation (ICMS) and if VBSNC application of astrocyte inhibitor (Methionine Sulfoximine, MSO) modulates this effect. Under general anaesthesia, male rats were implanted with electromyographic (EMG) electrodes into the anterior digastric (AD) jaw-opening muscles. Following craniotomy, a microelectrode was positioned in the left face-M1 (<2.4mm depth) at a site from which ICMS (35ms train, 12x0.2ms pulses, 333Hz) evoked low-threshold (≤30μA) AD EMG activities. Baseline ICMS thresholds were monitored for 30min, then MO (N=8)(or saline N=8) was applied to previously exposed pulp. In other rats (N=6), 0.1mM MSO (or saline N=6) was applied to VBSNC 15min after MO application. ICMS thresholds were monitored every 10min for 120min after MO/saline pulpal application. AD ICMS thresholds significantly increased within 15min of MO (but not saline) pulp application (46%; ANOVA, post-hoc Bonferroni: p=0.001) compared to baseline. The decreased face-M1 excitability was normalised to baseline levels following VBSNC application of MSO. Our findings suggest that motor disturbances associated clinically with dental pain may involve decreased face-M1 excitability modulated by VBSNC astrocytes. Support:CIHR;Rosentadt Funds

3-D-129 Visuo-oculomotor abilities of a single hemisphere - a study of bilateral saccadic eye movement corollary discharges in hemidecorticate subjects

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The study of hemidecorticate subjects has allowed us to discover that a single hemisphere is capable of generating accurate bilateral saccades, a task thought before to be governed only by the contralateral hemisphere. Hemidecorticate subjects are able to monitor eye position during smooth pursuit movements in either direction using a corollary discharge (CD) signal to determine where the eyes have moved in space. Since smooth pursuit is believed to be controlled by the ipsilateral hemisphere, it is surprising that these subjects were able to perform well bilaterally. With our current study, we sought to determine whether the hemidecorticate brain is capable of generating, transmitting and interpreting a similarly effective CD signal for bilateral saccadic eye movements. The literature suggests that lesions of the parietal areas

cause marked deficiencies in saccadic eye movement monitoring contralesionally. Using a novel version of the double-step task, we have shown that a single hemisphere does in fact monitor previous eye movements bilaterally, and integrate this information into subsequent movements in the dark. While their performance is markedly worse than controls, they are surprisingly more capable than subjects with isolated unilateral parietal lesions performing similar tasks. These findings suggest that further research into the relationship between performance and the extent of the lesion should be conducted; it is possible that larger cortical lesions induce greater plasticity in remaining brain areas, an idea that could have profound clinical implications.

3-D-130 Effects of Sleep Deprivation on Molecular Markers of Muscle Regeneration Following Injury

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Introduction: Skeletal muscles exhibit the ability to rapidly repair damage following muscular injury. The efficacy of muscle repair is sensitive to changes in neural input. During sleep, neuromuscular activation is generally reduced; however, the role for sleep in influencing muscle repair is unknown. Our aim was to investigate the effects of sleep loss on molecular and histological markers of muscle repair following myotoxic injury. Methods: Male rats were instrumented with electroencephalogram and electromyogram electrodes to monitor sleep-wake states. Rats were injected with 1.5% bupivacaine into muscles of interest. Rats were either sleep-deprived for 8 hours or served as time controls, and were subsequently sacrificed at 2, 7 or 14 days post-injury. Muscle repair was assessed by immunoblot assay of molecular repair markers (MyoD and myogenin). Results: Following myotoxic injury, acute sleep deprivation suppressed molecular markers of muscle repair; specifically, MyoD expression in the masseter was significantly suppressed at 2 and 7 days post-injury, whereas myogenin was suppressed after 2 days. Conclusions: We demonstrate that perturbed muscle regulation during sleep loss may adversely affect muscle repair following injury. Specifically, sleep loss results in suppressed protein expression of molecular repair factors. Together, these results implicate the dysregulation of motor control during sleep deprivation as a promising avenue for exploring the interaction between sleep and muscle repair.

3-D-131 Characterization of the antinociceptive effects of an MAO inhibitor and its metabolite

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Central sensitization is a critical mechanism underlying many chronic pain states. We have recently observed that the monoamine oxidase inhibitor phenelzine (PLZ) can decrease the tactile hypersensitivity that develops in a mouse model of Multiple Sclerosis, experimental autoimmune encephalomyelitis. We have now carried out experiments using a model of tonic nociceptive pain, the formalin test. We examined the effects of PLZ and its metabolite phenylethylidenehydrazine (PEH), a novel GABA transaminase inhibitor, on formalin-evoked nociceptive behaviours in male and female mice. We find that the antinociceptive effects of PLZ and PEH appear to be gender-dependent. Using immunocytochemistry we set out to identify the cellular and molecular changes associated with PLZ- and PEH- mediated antinociception that may account for our behavioural observations. c-FOS labelling in the spinal cords of animals treated with PLZ or PEH was not significantly different from that observed in vehicle (saline)-treated controls. GABA-like immunoreactivity was markedly larger in the spinal cords of PLZ- and PEH-treated animals relative to vehicle-treated controls. Finally, 5-HT-like immunoreactivity was significantly greater in the spinal cords of PLZ-treated females, but not males, relative to vehicle-treated controls. Our results

suggest that potentiation of serotonergic and GABAergic transmission in the spinal cord may be a major contributor to PLZ- and PEH-mediated antinociception.

3-D-132 Preserved grip scaling to visual size despite non-veridical haptic feedback in a patient with visual form agnosia

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One of the foundational observations supporting the two-visual-systems model (Goodale and Milner, 1992) is patient DF's preserved ability to adjust her in-flight grip aperture to target size when reaching out to pick up the target despite her profound deficits in judging the size of the target either verbally or by indicating its size with her finger and thumb. DF's deficits in object perception are attributed to the extensive bilateral lesions to her ventral stream, whereas her spared object size processing for goal-directed action, like grasping, is attributed to her relatively spared dorsal stream. Recently, however, Schenk (2012) has shown, using a mirror apparatus, that when the target is not felt at the end of a grasp, DF does not scale her grasp to target size, yet controls continue to do so. Schenk argued that DF's grip scaling must, therefore, be calibrated by both vision and haptics. Here, in a set of new experiments with the mirror apparatus, we show that DF continues to scale her grip to changes in the viewed size of the goal object despite the felt size of the object remaining constant, suggesting that the mere presence of a felt object, rather than veridical haptic calibration, is sufficient for dorsal-stream mediated grip scaling. Furthermore, we show that normally-sighted individuals exhibit sharper size scaling to target size when the target is not felt than when it is, suggesting that removing haptic feedback induces pantomime-like grasps - grasps which DF was previously shown to perform inadequately and one that likely relies on an intact ventral stream.

E – Homeostatic and Neuroendoctrine Systems

3-E-133 Androgen Effects on Dendritic Spine and Mossy Fiber Plasticity in the Male Rat Hippocampus

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Androgen effects on the hippocampus remain poorly understood. Though orchidectomy (ORCH) decreases spine synapse density in stratum radiatum of CA1, studies on electrophysiology and androgen deprivation on cognitive function have yielded mixed results. We hypothesized that this variability might reflect heterogeneity in androgen effects on dendritic spine (DSD) and mossy fiber (MF) density in different regions of the hippocampus. We re-examined the effects of ORCH on DSD and spine length in the apical dendritic tree of pyramidal cells in CA1 and CA3, and also investigated MF density in CA3. Two months following ORCH, adult male rat hippocampi were golgi-impregnated. Females at metestrus and proestrus were also examined. DSD decreased significantly following ORCH on the apical dendrites of CA1 and CA3, but not to the extent observed in females. Females in metestrus had significantly lower DSD in most areas of CA1, as well as CA3. No significant changes were observed in spine length. MF density in stratum lucidum and stratum oriens was significantly greater in ORCH males compared to controls. In females, no significant differences were found. Decreased DSD after ORCH is consistent with reduced performance in some learning and memory tasks. Possible compensatory changes, e.g. increased MF density, may help explain why androgen-deprived rats do not exhibit impaired performance on all tasks. [Supported by NSERC 197293-2007]

3-E-134 Characterization of corticotropin-releasing hormone neurons in the paraventricular nucleus of the hypothalamus of Crh-IRES-Cre mutant mice

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Corticotropin-releasing hormone (CRH)-containing neurons in the paraventricular nucleus of the hypothalamus (PVN) are the principal regulators of the endocrine response to stress. Previously, physiological studies focusing on CRH neurons have had access to a very limited toolbox. Here, we utilized a recently developed Crh-IRES-Cre driver mouse line crossed with the Ai14 reporter mice to visualize CRH neurons via Cre-driven expression of tdTomato. We found that tdTomato expression reliably and robustly provided morphological detail to a population of PVN neurons without signal-amplification methods. We assessed, using immunohistochemistry, whether tdTomato expression recapitulated that of CRH protein. We found that a large majority of tdTomato+ neurons were also immunreactive for CRH (80.5 %), while only a few co-expressed other neuropeptides abundant in the PVN, such as vasopressin (4.9 %) or oxytocin (3.0 %). Furthermore, we found c-Fos, a neuronal activation marker was detected in nearly all tdTomato+ cells in response to an acute forced-swim stress (89.5 %). We report that tdTomato+ neurons exhibit an electrophysiological fingerprint similar to that of rat parvocellular neuroendocrine cells (NCs), and distinct from tdTomato- putative magnocellular NCs. Finally we found that their activity is readily manipulated by a viral Cre-driver dependent expression of channelrhodopsin. Together, these results show basic cellular properties of mouse CRH neurons, and demonstrate effective targeting and manipulation of these cells through use of Crh-IRES-Cre;Ai14 mice.

3-E-135 Distribution of L-Amino acid decarboxylase- and tyrosine hydroxylase-immunoreactive cells in the naked mole-rat brain

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The distribution and projections of dopaminergic neurons contributes to species-specific sociosexual organization. This may be relevant for naked mole-rats (Heterocephalus glaber), which are eusocial mammals. They live in large social colonies and restrict reproduction to a single dominant female and 1-3 males in each colony. The remainder of the animals, which can be up to 300 individuals, are reproductively suppressed subordinates. An important indicator that cells are producing dopamine is the presence of both tyrosine hydroxylase (TH), which is necessary for conversion of L-Tyrosine to L-DOPA, and aromatic l-amino acid decarboxylase (AAAD), which is responsible for conversion of L-DOPA to dopamine. The present study characterizes populations of cells in the naked mole-rat brain that are immunoreactive for TH and/or AAAD. Our findings demonstrate the presence of TH, AAAD, and double-labelled cells in the substantia nigra (SN), the ventral tegmental area, the anteroventral periventricular nucleus, the paraventricular nucleus of the hypothalamus, the medial preoptic area, the arcuate nucleus and the zona incerta. There are also AAAD-labelled cells throughout the cortex and in the lateral habenula, the medial septum, the paraventricular nucleus of the thalamus, the bed nucleus of the anterior commissure, as well as a small amount of staining in the bed nucleus of the stria terminalis and medial amygdala. We also report extensive TH fibres in the caudate putamen, the ventral pallidum, the nucleus accumbens, the zona incerta, the lateral septum, and the SN.

3-E-136 Sexual behaviors in the ovariectomized rat are sensitized by chronic estradiol treatment and attenuated by vaginocervical stimulation

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Acute estradiol administered to the ovariectomized (OVX) rat partially reinstates sexual behavior. We have shown that 10µg (but not 2µg) of estradiol benzoate (EB) administered alone every 4 days to the OVX rat results in the rapid sensitization of

sexual behaviors such that lordosis is potentiated and appetitive behaviors emerge as early as the second test, and the effect is maintained until at least the eigth test. Here, we tested whether the sensitization is solely dependent on estradiol, or whether repeated copulation also plays a role. Sexually-experienced OVX rats were treated with either 2µg or 10µg EB 48 hours prior to the first and eighth copulatory test sessions. Manipulations were made on Tests 2-7: females were either treated with oil, 2µg EB, or 10µg EB and placed in the uni-level pacing chamber alone (OA, 2A, 10A respectively), or treated with 10µg EB and allowed to copulate with a sexually vigorous male (10C). Sensitization did not occur in OA. However, both 10A, and those treated with 2µg EB (2A), a dose thought to be too low to elicit sexual behavior on its own, developed sensitization. Moreover, sensitization was attenuated in 10C compared to 10A. We subsequently found that the attenuation is due to vaginocervical stimulation. We are currently investigating whether glutamate receptors within the ventrolateral portion of the ventromedial hypothalamus are involved in this attenuation, since glutamate is thought to be an inhibitory signal to sexual behavior in this region.

3-E-137 Fluoxetine Hydrochloride (Prozac) Decreases Stereotypical Behaviours in Subordinate Naked Mole-Rats, Heterocephalus glaber

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Naked mole-rats are eusocial rodents that live in large subterranean colonies with a strict reproductive and social hierarchy. Reproduction is restricted to a single breeding female and 1-3 breeding males; all other colony members are non-reproductive subordinates. Subordinates contribute to the colony in the form of tunnel maintenance and foraging, which manifests as compulsive, stereotypical digging. These behaviours that, to a certain extent, define their social role or status in a colony may be altered by fluoxetine hydrochloride (FLX), which plays an important role in the prevention of stereotypies in other species. In this study, we aimed to determine if FLX alters stereotypical behaviours in naked mole-rats and whether this results in a change in status of members in the colony. Specifically, 16 adult subordinates received a daily intraperitoneal injection of FLX (10mg/kg) for 4 weeks and another 16 age- and weight-matched control subordinates received 0.9% sterile saline (10ml/kg). Stereotypical behaviours of subordinates displayed in the colony were compared before, during and after the chronic dosing regimen. Significant weight gain for control animals compared to animals who received FLX demonstrated a successful physiological drug manipulation. Our findings revealed that chronic exposure to FLX decreases general activity and specific stereotypies (e.g., digging and climbing) compared to control animals without concomitant changes in social status. The results support the hypothesis that FLX administration decreases stereotypy in subordinate naked mole-rats.

3-E-138 Activity-induced Arc expression in newborn neurons following chronic stress

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Spatial exploration induces the expression of activity-regulated cytoskeletal-associated protein (Arc) in newborn neurons of the dentate gyrus. Arc is an immediate early gene coupled to neural activity and involved in neuronal plasticity. It is not known whether chronic stress has a detrimental effect on spatial exploration-induced Arc expression in newborn neurons of the dentate gyrus. Thus, the present experiment explores this question. Following 10 days BrdU injection (50 mg/kg), rats were administered with either corticosterone (CORT, 40 mg/kg) or vehicle for 28 consecutive days. Spatial learning and memory was explored eight days following the last CORT/vehicle injection using the Morris Water Maze. Chronic CORT injection followed by an 8-day wash-out period had no influence on water maze training. Both groups of rats also learned the reversal training in the water

maze equally well. One week following the water maze training, rats were sacrificed following spatial exploration of a novel environment. The pattern of Arc expression is being explored in both newborn and developmentally born granule cells.

3-E-139 The relationship between innate sucrose preferences and intake escalation induced by restricted access in rats and its effect on weight gain.

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Obesity is increasing and may be associated with elevated intake of sugary drinks; suggesting exploring, in rat models the effect of sugary beverage intake on weight gain. Male Sprague-Dawley rats show considerable variance in sucrose intake, drinking between 75 and 160g a day: averaging ~120g of 4% sucrose per day. When access is restricted to 24h out of every 72h rats drink ~240g of 4% sucrose. It is not clear if innate sucrose preferences are correlated to the consumption increase shown when access is restricted. Restricted access that results in binge-like consumption (doubling typical intake) may be associated with increased weight gain. The current study considered the relationship between innate sucrose preference and the consumption escalation seen when access is restricted as well as sucrose consumptions impact on weight in ad lib fed rats. Rats were randomly assigned to daily or restricted (once every third day) access to 4% sucrose for 40 days. Subsequently, the two groups were split and rats received either daily or restricted access. Rats showed considerable innate differences in sucrose preference which was not correlated to intake escalation induced by restricted access, suggesting the increase was due to a different mechanism than that responsible for the variance in initial preference. The access manipulations of sucrose solution had no impact on weight gain, all rats gained weight at a comparable rate to non-sucrose controls. Binge-like consumption of 4% sugar solution does not necessarily enhance weight gain.

F – Cognition and Behaviour

3-F-140 Effects of housing conditions on neurogenesis in black-capped chickadees (Poecile atricapillus)

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In chickadees, captivity leads to suppressed neurogenesis in the hippocampal complex compared to free-ranging birds (Barnea & Nottebohm, 1996). It is not known whether varying housing condition influences the degree to which neurogenesis is suppressed. We captured birds during winter and injected them with the cell birth marker bromodeoxyuridine (BrdU). We then housed birds for 6 weeks under three different conditions: outdoor aviary, indoor aviary, and indoor cage. Behaviours such as activity levels, vocalizing, and food storing were assessed in regular observation periods twice per week per bird; at the end of the 6 weeks brain tissue was collected and we assessed neuronal proliferation and survival as well as hippocampal volume. Results from this study will allow us to determine the effects of housing condition on neurogenesis while considering associated factors including behavioural differences and climate. These results will provide insight to what factors underly differences in neurogenesis between captive and free-flying birds. Further, results will aid in understanding the influence of environmental context in field and laboratory studies using songbirds.

3-F-141 Exploring sex differences in the Morris water maze as a consequence of early life nicotine exposure in a model of preterm birth

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Maternal smoking is viewed as a substantial contributor to fetal and infant morbidity and is the leading cause of infant mortality in developed countries, including Canada. These occur in part by increasing the incidence of very-low-birth-weight

births and the risk of premature birth. In an effort to reduce tobacco exposure in the general population and particularly during pregnancy, a variety of treatment options have been proposed and used, including nicotine replacement. The effects of this pharmacological therapy on brain and behaviour is still not well understood and even less so in preterm infants. In our model of preterm birth, we find that male rats are more susceptible to the effects of muscimol early in life. Thus, we wanted to explore whether nicotine exposure in this preterm birth model would yield any sex differences in cognitive behaviour. Male and female rats were treated with either saline/saline, saline/muscimol, nicotine/saline or nicotine/muscimol on the first two days of life. Pre-testing to reduce anxiety associated with the Morris water maze revealed that overall males learned faster, though males treated with saline/muscimol tended to take a bit longer. No treatment or sex differences were apparent in either of the three blocks of testing, with all animals showing a reduction in latency to find the hidden platform over time. These data are important to show that neonatal nicotine exposure under our protocol, in a model of preterm birth, does not affect memory in the peri-adolescent male and female rat.

3-F-142 Nicotine's Effect on Electrocortical Arousal and its Modulation by Catechol-O-Methyl-Transferase (COMT) Genotype

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Schizophrenia is a cognitive disorder that is highly comorbid with nicotine dependence, which has been associated with reduced nicotinic acetylcholine subunit receptors (nAChRs). nAChRs modulate multiple neurotransmitters, including dopamine. Dopamine abnormalities found in SZ have encouraged investigations of COMT, the principal enzyme involved in synaptic dopamine degradation in frontal brain regions. In humans, the main polymorphism associated with COMT is Val158Met. Carriers of the homozygous Val allele (associated with increased dopamine metabolism) are reported as performing poorly on cognitive tasks and have lower levels of prefrontal dopamine compared to Met carriers. Nicotine has been associated with increases in electrocortical arousal, and may be used to increase activation in individuals with low dopaminergic tone. Our study looked at the effects of nicotine on brain state arousal in COMT genotypes using quantitative EEG, hypothesizing that nicotine would significantly increase activation in Val carriers. In a sample of 57 healthy controls, reduced activation (diminished beta 1) was evident in the Val genotype during placebo, and nicotine acted selectively to increase arousal (greater alpha 2 and beta 1) in Met carriers. These findings confirm an association between low dopaminergic tone in the Val variant with brain hypoactivation and support the notion that nicotine induced activation is baseline dependent, but did not support the hypothesis that activation is selective in individuals with low prefrontal dopamine tone.

3-F-143 Recollection of Narrative Information Benefits from Self-Referential Encoding in Healthy Aging

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The Self-Reference Effect (SRE), enhanced memory for information encoded through self-attribution, has been exhibited in young and older adults. Past studies, however, primarily used trait adjectives as stimuli. The present study sought to examine whether the SRE can be extended to memory for narratives, which has been shown to decline even with healthy aging. Twenty younger (age 18-26) and 20 older (age 65-79) adults encoded short narratives by deciding: 1) whether they could easily imagine themselves as the protagonist (self-reference condition); 2) whether the event described was positive (semantic condition); or 3)

whether the word "the" appeared more than four times (structural condition). Results indicated that although self-referential and semantic encoding benefitted memory to a similar extent when measured by a recognition task, an accompanying remember/know decision indicated that self-referential processing promoted recollection of narrative material more than the other encoding conditions. Further, in a recall test, the SRE was clearly evident for narratives: memory was greatest in the self-reference condition compared to the other two conditions. Performance in the structural condition was worse than in the others. Although younger adults outperformed their older counterparts on both overall recognition and recall of narratives, the SRE promoted recall and recollective retrieval experience, capacities shown to decline with aging. The SRE may therefore provide an effective intervention strategy for enhancing recall and episodic re-experiencing of narrative info.

3-F-144 Temporally and spatially predictive saccades and their neural correlates

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Prediction is the process of using information from the past or present to guide future behaviour; it is needed to compensate for neural delays between a sensory input and an appropriate motor output. We designed a task to clarify the behavioural control and the neural correlates involved in temporal and spatial prediction. A task involving temporally and spatially (un)predictive saccades was employed in the MRI where 4 conditions were tested: spatially/ temporally predictive (STP), temporally predictive/spatially unpredictive (TP), spatially predictive/ temporally unpredictive (SP), and spatially/temporally unpredictive (STU). Preliminary data from 6 subjects (aged: 19-25) show distinct behavioural differences between conditions. All subjects showed primarily predictive saccades (saccadic reaction time(SRT)<100ms) in the STP condition, while in the STU condition primarily reactive saccades (SRT>100ms) were observed. Furthermore, the average SRT of the SP condition fell between the average SRTs of the STP and STU conditions. Two distinct strategies were observed in the TP condition. Some subjects exhibited primarily predictive saccades (n=3), with an average SRT falling between the SRTs of the STP and STU conditions, but the other group triggered primarily reactive saccades (n=3) where the average SRT was similar to the STU condition. Analysis of functional imaging data of subjects exhibiting primarily predictive behaviour show bilateral FEF activation prevalent during spatially predictive conditions and select cerebellar activation during temporally predictive conditions.

3-F-145 The role of the histaminergic H1, H2, and H3 receptors of the lateral septum in rats' anxiety-related behaviors in two animal models of anxiety

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The neural histaminergic system is involved in a range of physiological processes, including anxiety. Histaminergic neurons are localized in the tuberomammillary nucleus of the posterior hypothalamus and share bidirectional connections with the lateral septum, an area known to regulate anxiety. The current study examined whether the histaminergic system of the lateral septum regulates rats' defensive behaviors in two animal models of anxiety, the elevated plus maze (EPM) and novelty-induced suppression of feeding paradigm (NISF). We found that histamine (1.0µg and 5.0µg) when bilaterally infused into the lateral septum decreased rats' defensive behaviors in the EPM (both doses) and NISF (1.0µg only). Additional experiments found that pre-infusions of the H1 and H2 antagonists, pyrilamine (20µg) and ranitidine (20µg) respectively, attenuated the anxiolytic-like effects of intra-LS histamine (1.0µg) in the NISF but not in the EPM. In contrast, pre-infusions of the H3 antagonist ciproxifan (200pg) reversed the anxiolytic-like effects of intra-LS histamine in the EPM but not in the NISF. This double dissociation

suggests that these receptors differentially regulate rats' defensive behaviors in the EPM and NISF - more specifically, avoidance of open spaces and neophagia respectively.

3-F-146 Increased Activity of Frontal and Limbic Regions to Emotional Stimuli in Children At-Risk for Anxiety Disorders

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Introduction: Neuroimaging studies of children with anxiety disorders are limited and to date no study has investigated high-risk populations. The first objective was to examine the prevalence of psychiatric disorders in high-risk subjects. The second objective was to examine the activity of emotion processing brain regions in high-risk children using functional magnetic resonance imaging (fMRI). Methods: High-risk children (n=20) who had at least one parent with a primary diagnosis of social phobia and normal-risk control children (n=19) participated in the study. Children and parents were assessed using structured clinical interviews. Using fMRI, we measured the blood oxygenation level dependent response while children were exposed to different emotional facial stimuli. Results: We found the prevalence of anxiety disorders to be elevated in high-risk children with 77% meeting criteria for a lifetime psychiatric disorder. High-risk children had significantly higher levels of anxiety and depressive symptoms relative to normal-risk children on self-report and clinician-rated measures. Our fMRI analysis revealed greater activation of several frontal and limbic regions in high-risk subjects relative to normal-risk subjects during the presentation of emotional facial stimuli. These regions included the prefrontal cortex, anterior cingulate, hippocampus, insula and basal ganglia. Discussion: To our knowledge this is the first study to characterize a sample of children at-risk for anxiety disorders using clinical and neuroimaging data.

3-F-147 Semantic Memory Structure Abnormalities in a Case of Developmental Amnesia

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Developmental Amnesia (DA) is a strong source of evidence for the notion that episodic and semantic memory are dissociable systems that develop independently, with hippocampal integrity necessary for episodic memories only. While it has been demonstrated that core semantics can be learned even without an intact hippocampus, there is no research directly addressing the structural relationships among semantic representations acquired in DA. Inasmuch as there are suggestions that re-organization processes known to support episodic memory may also play a role in general knowledge integration, it seems likely that semantic representations differ in their structure when acquired against the background of episodic memory impairment. We tested a developmental amnesic (HC) using semantic memory tasks based on a normative database of concrete concepts. Unlike typical neuropsychological tests that primarily tap into discrete aspects of semantic memory, our tasks required comparisons among similar concepts in terms of their typicality for semantic categories, and also their familiarity. We probed relationships between concepts and their features, and between related concepts, in two generation tasks. Preliminary analyses suggest that HC's category structure (typicality rating) differs from that of age- and education-matched controls. In DA, abnormalities in structural relationships may be present even when concepts have apparently been acquired successfully. These data suggest that the hippocampus may play a role in the development of fine-grained structural semantic relationships.

3-F-148 The effects of access conditions and quinine adulteration on sucrose consumption

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In many drug and non-drug protocols intermittent access to a reward produces large increases in consumption (Corwin, et al., 1998). Rats with ad libitum access to food and water will consume significantly more 4% sucrose solution when it is presented intermittently (24h every third day) as opposed to continuously. This access-induced consumption difference is masked with 8% or 16% sucrose solutions. When these animals are given access to 4% sucrose, a significant consumption difference emerges immediately. The lack of an initial consumption difference may be attributed to the solutions higher caloric value. The current study investigates the possibility that the addition of quinine (0.005%) to the sucrose will reduce intake, alleviating caloric constraints, and permit the emergence of an access-induced consumption difference. Sprague-Dawley rats (N=64) were assigned, on the basis of initial 4% sucrose consumption, to intermittent (every 3rd day) or continuous access of 4%, 8%, with or without quinine added sucrose solution. The addition of quinine to sucrose solution produced a global decrease in consumption that was more pronounced in 4% than 8% sucrose. The typical consumption difference seen with the access manipulation in 4% animals persisted in the quinine condition. With the 8% solutions the difference in consumption between intermittent and continuous access was not evident in either condition. This suggests that the consumption differences created by access conditions, sucrose concentration and flavor manipulations differ in their etiology.

3-F-149 The effect of sleep deprivation on Neuroligin protein levels in different brain regions

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Background: Sleep loss results in important changes in synaptic properties, and we have previously shown that it affects the forebrain expression of Neuroligin 1 (NLGN1), a synaptic adhesion molecule involved in synaptic plasticity. In this study, we aimed to determine the effect of sleep deprivation (SD) on NLGN1 synaptic level in different brain regions, as well as its impact on other NLGNs. Methodology: C57BL/6J male mice were submitted to a 6h SD performed by gentle handling starting at light onset. At the end of the SD, mice were sacrificed at the same time as non-sleep deprived controls, and brains were immediately dissected to sample the cerebral cortex, the hippocampus, and a region covering the thalamus and hypothalamus. Synaptoneurosomal protein extraction was performed for the 3 brain regions, followed by western blots for identification of NLGNs. Results: Preliminary data indicate that SD does not change the synaptic levels of NLGN1 and NLGN2 in the cerebral cortex, the hippocampus and the thalamus/hypothalamus region. The effect of SD on NLGN3 level is currently being quantified. Conclusion: These results suggest that the acute effect of sleep loss on NLGN1 may primarily impact other brain regions, such as the striatum, or that the effect is somewhat more global being only revealed using whole brain extracts.

3-F-150 Estrogen receptor agonists rapidly affect learning in the social transmission of food preferences task in female mice

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The social transmission of food preferences (STFP) is a way to test social learning in rodents. In the STFP, a mouse learns about a novel flavoured food it smells on the breath of a conspecific and subsequently prefers that food. Estrogens mediate performance on this task on a long-term, genomic time scale and on a rapid, non-genomic time scale. In the long-term, estrogen receptor (ER) β agonists improve, while ERα agonists impair, performance on the STFP. To examine early effects of estrogens, we focused on the first hour after hormone treatment with a modified STFP paradigm to differentiate impairing or improving effects. In an easy version, control animals readily learn, but

show no learning in a difficult version. We found 17β-estradiol improves learning on the difficult STFP within 75 minutes. We administered selective ER agonists subcutaneously to the observer mouse 15 minutes prior to social interaction to investigate early effects of ERα, ERβ, and the G-protein coupled ER (GPER1) in the STFP. We used the ERα agonist propyl pyrazole triol (PPT) and ERβ agonist diarylpropionitrile (DPN) at 30, 50, 75, and 150ug/mouse and 30, 90, 180, and 900ug of the GPER1 agonist G1. Similar to the long-term effects, 30ug PPT blocked learning in the easy task, but DPN did not improve it in the difficult task. G1 (180ug) improved social learning on the difficult STFP, similar to estradiol. GPER1 may therefore mediate the early improvements of estradiol, while ERα activation can impair social learning on both rapid and long-term time scales.

3-F-151 Searching for the engram: Enhanced pyramidal cell responses in the piriform cortex parallel an extended early odor preference memory in rats?

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Early odor preference learning in neonate rats provides an ideal model to study memory mechanisms. In this model, tactile stimulation (stroking) is paired with a naturally aversive odor, peppermint. A single 10 min pairing of the two leads to a preference memory for peppermint that can be detected 24 hrs later. Our recent work has provided evidence for the involvement of the piriform cortex (PC), the primary olfactory cortex, in the 24 hr odor preference memory. One trial learning enhanced synaptic transmission at the lateral olfactory tract (LOT) to pyramidal cell synapses 24 hr post-training. In this study, we examine whether the time course of synaptic changes in the PC parallels behaviorally detectable memory. Neonatal rats (within one week old) underwent odor training, with single nostril occluded. Animals were then sacrificed at various time points for brain slicing and electrophysiological recording. We measured input-output relationship (presynaptic volley vs. slope of field excitatory postsynaptic potential; fEPSP) and paired pulse ratios of fEPSPs at the LOT synapses. Preliminary data show that at 48 hr following one trial training, no synaptic potentiation was observed in either the trained or the occluded hemisphere, corresponding to an extinction of the odor preference memory at 48 hr. However, when the odor preference memory was extended to 48 hr following a multi-trial training, a trend of enhanced LOT synaptic transmission was observed at 48 hr. These data suggest odor memories in rat pups are paralleled and supported by synaptic changes in the PC.

3-F-152 Sleep architecture in mice lacking the EphA4 receptor

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Introduction: Sleep is required in mammals, and its recovery aspect was hypothesized to depend on mechanisms controlling synaptic strength. The EphA4 receptor (EphA4) is an adhesion molecule which has been implicated in the regulation of synaptic function and plasticity. The aim of the study is to understand the role of EphA4 in sleep regulation. Methodology: To do so, we analyzed vigilance states (wakefulness, non-Rapid Eye Movement [REM] and REM sleep) duration using electroencephalography [EEG] in mice lacking EphA4 (generously provided by K. Murai, and bred on site). Ten-week-old mice from the three genotypes (wild-type [WT], heterozygous [het] and homozygous mutants [KO]) were implanted with EEG electrodes under deep ketamine/xylazine anesthesia. EEG activity was recorded during 2 baseline days. Vigilance states were visually identified and assigned to 4-sec epochs. Preliminary analysis of baseline day 2 in 8 WT, 10 het and 6 KO are presented here. Results: During the full 24h, EphA4 KO mice were significantly more awake then WT and het mice. KO mice also showed less REM sleep than WT. When looking specifically at the rest

period (12h light), KO also showed more wakefulness than WT and het, but the change in REM sleep time was not significant. Further analyses are currently underway. Discussion: These preliminary results suggest that EphA4 may act to favor sleep. Current experiments are assessing the effect of the duration of wakefulness on gene and protein expression of EphA4.

3-F-153 Intermittent Environmental Enrichment: A Novel Strategy For Untangling The Variables Regulating Adult Hippocampal Neurogenesis

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Environmental enrichment (EE), including running, environmental complexity, social interactions and stress, has powerful effects on brain physiology. However, the relative contributions of the individual EE variables are a longstanding issue that remains poorly understood. To help untangle the effects of these variables, we developed a novel experimental paradigm based on intermittent exposure to EE, and we used this model to evaluate the impacts of EE variables on adult hippocampal neurogenesis. Adult male CD1 mice were alternated daily between two environments for 4 weeks; by comparing groups in which only one of the two environments differed, EE variables could be effectively isolated and their impact on neurogenesis assessed. We found that intermittent voluntary exercise was sufficient to maximally increase the proliferation, neuroblast and post-mitotic neuron stages of neurogenesis, and to elicit changes in depolarization-associated c-fos expression within the dentate gyrus. Surprisingly, neither social enrichment nor increased levels of stress-associated plasma corticosterone demonstrated impacts on neurogenesis. Moreover, environmental complexity effectively buffered corticosterone increases, yet did not affect basal or running-induced neurogenesis. Mouse strain, handling and type of running apparatus were excluded as potential confounding variables. These findings help resolve the contributions of single variables to adult neurogenesis, and this intermittent EE paradigm will serve as a useful tool for rationally designing more effective and targeted EE approaches.

3-F-154 Ketamine enhances destabilization of fear memory

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We have hypothesized that one mechanism underlying the development and persistence of schizophrenic symptoms maybe dysregulated reconsolidation. A recent study in humans found that reactivation of a fear associated cue in the presence of an acute sub-anesthetic psychotomimetic, ketamine, enhanced subsequent responses to that cue. We have argued that this effect was due to ketamine-induced alterations in prediction error (PE). It has also been proposed that the destabilization of a memory, which requires subsequent reconsolidation, requires the presence of new information. We therefore investigated whether ketamine would augment fear memory reconsolidation in the rat. We found that an acute sub-anesthetic dose of ketamine administered prior to but not immediately following fear memory reactivation resulted in increases in post-reactivation long-term memory measured by freezing. Subsequent experiments investigated pharmacological blockade of this effect and its neuroanatomical locus of action.

3-F-155 Imaging Ca2+ activity in GABAergic septo-hippocampal projecting axons during awake behaviour

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The septo-hippocampal pathway, connecting cholinergic and GABAergic neurons in the medial septum with hippocampal neurons, has been hypothesized to play an important role in

hippocampal dependent learning. Whereas cholinergic axons in hippocampal area CA1 appear to influence neurons through volume transmission, large populations of GABAergic axons selectively innervate inhibitory hippocampal interneurons with classical synapses. To characterize the population dynamics of this pojection in awake behaving animals, we developed a system for 2-photon imaging of GABAergic septo-hippocampal axon terminals in the hippocampus of head-fixed mice walking on a treadmill while engaged with external sensory stimuli. We virally expressed GCaMP.5 in GABAergic septal neurons, and imaged Ca2 dynamics in their identifiable axonal boutons making putative synaptic contacts with somatic or dendritic profiles of tdTomato-labeled interneurons in hippocampal area CA1. We found subgroups of boutons that behaved coherently during resting, locomotion, and/or sensory stimulation, but were silent under anesthesia. With local application of baclofen through a hole in the imaging window, we found that GABA-B receptor-mediated presynaptic inhibition modulates the amplitude, but not the tuning properties, of septo-hippocampal bouton responses. These results demonstrate that GABAergic boutons from the medial septum provide complex behavioral state- and stimulus-dependent inhibition to hippocampal interneurons.

3-F-156 Cholinergic Tone and Attention: A possible Role of the a7 Nicotinic Acetylcholine Receptor

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Acetylcholine (ACh) is one of the main neuromodulators in the mammalian central nervous system (CNS). Cholinergic activity has been suggested to regulate attentional processing, by generating top-down control of attention, including orienting towards the stimulus and stimulus discrimination. The mechanisms underlying these processes are still however poorly understood and there is controversy regarding the specific roles of α7 nicotinic acetylcholine receptors (α7nAChR) in the regulation of attention. Moreover, the potential roles of cholinergic neurons in attentional processing have been examined mainly by immunolesion of basal forebrain cholinergic neurons. However, recent studies have shown that cholinergic neurons can also release glutamate, which would also be affected also by immunolesion. We measured attention performance by using the the 5-choice serial reaction time task (5-CSRT) paradigm in touchscreens. Administration of galantamine in wild-type mice improved their performance during demanding attention tasks. Administration of a α7nAChR partial agonist also improved performance of wild-type mice in the 5-CSRT. To examine the specific contribution of cholinergic tone for attention processing we then selectively impaired release of ACh from forebrain cholinergic projection neurons by genetically-targeting the Vesicular Acetylcholine Transporter (VAChT), a protein required for synaptic storage and release of ACh. We find that VAChT-targeted mice takes much longer to reach criteria in the 5-CSRT and have profound attention deficits in the 5-CSRT.

3-F-157 Effects of early life nicotine exposure on a measure of anxiety and locomotion, in an animal model of preterm birth

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Fetal and neonatal exposure to nicotine remains a problem in our society. While the incidence of smoking during pregnancy has decreased, the population is now faced with an increase in nicotine exposure during this time due to the enhanced use of nicotine replacement therapy products. Nicotine replacement therapy in the form of gum, inhaler or trans-dermal patch is used to help individuals quit smoking. While deleterious effects of cigarettes/ tobacco are well documented, information is lacking as to the effects of nicotine replacement therapy on the developing fetus/neonate. Given the increased risk of premature birth with maternal smoking, the objective of the proposed research is to investigate the behavioural consequences of

early life nicotine exposure, in a model of preterm birth. Male and female rats received the following treatments on the first two days of life 1.saline/saline, 2.muscimol/saline, 3.saline/nicotine or muscimol/nicotine. Animals were weaned from the dam on postnatal day 21 and housed two per same sex cage until the time of behavioural testing that began on postnatal day 30 (Morris water maze -see submitted abstract). Behaviour in the open field was assessed on postnatal day 34. While sex differences in behaviour are not readily apparent, females did tend to spend more time grooming, a behaviour particularly apparent in the muscimol/nicotine treated females. These data are a first step in better understanding the long term effects of nicotine exposure in a preterm model.

3-F-158 Dissociations in future imagining, time perspective, and delay and probability discounting in episodic amnesia

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Recollecting past experiences and imagining future experiences both rely on a common network of brain structures including those in the medial temporal lobe (MTL). However, preliminary findings show that a person with episodic amnesia who is unable to imagine future events can nonetheless make future-oriented financial decisions. Thus, future-oriented thinking does not appear to be a unitary construct, and some forms of future thinking may not require MTL-mediated future imagining. Here we investigated other forms of decision-making and future thinking in individuals with extensive MTL damage and age-matched matched controls. Tests included an adapted version of the Autobiographical Interview to establish baselines of past recollection and future imagining (Addis et al., 2007), a probability discounting task to assess tendencies toward high-risk gambling and a delay discounting task to assess economic decision making as a function of time delay (Green & Myerson, 2004), and the Zimbardo Time Perspective Inventory to assess personal orientation toward the past, present, and future (Zimbardo & Boyd, 1999). The results revealed dissociable forms of future-thinking: all MTL individuals showed varying degrees of deficit in recollecting past experiences and imagining future experiences, but other aspects of their temporal thought and future-oriented decision-making were preserved. We conclude that episodic amnesia due to extensive MTL damage does not preclude consideration of future financial outcomes or personal identification with the past and future.

3-F-159 Novel Paradigm for Dissociating Executive Functions

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There has been controversy in cognitive psychology to whether executive functions are dissociable or unitary cognitive processes. This fractionation of executive control was supported by Miyake et al (2000) using factor-analytic methods to show that performance on multiple measures of executive control clustered around three factors: updating, inhibition and task switching. However, the tasks used to evaluate these functions were highly variable, with significant differences in perceptual and motor demands. No study to date has used carefully matched tasks to examine the relationship between updating, inhibition and task switching. Using a novel integrative paradigm that manipulates executive control demands while keeping all other aspects of stimulus processing constant, we were able to directly assess the dissociability of different executive functions. Participants fluidly switched between an updating task, an inhibition task and a perceptual control task. Initial behavioural findings support Miyake's model as reaction time and percent accuracy showed predicted within-subject variability in task performance amongst the three executive functions measured. If confirmed, these data will provide critical evidence supporting the fractionation of executive control functions. These results lay the foundation for a neuroimaging investigation to

examine the functional neuroanatomy of executive control processes in younger and older adults, thereby extending a recent meta-analytic investigation of these processes and neurocognitive aging (Turner and Spreng, 2012).

3-F-160 Involvement of hippocampal dopamine D1-type receptor in the social transmission of food preferences in male and female mice

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Dopamine is involved in the neural systems governing a number of behaviors, including food intake, social interactions, social learning, and memory processes. Recently we have shown the specific involvement of the dopamine D1-type receptor in social learning (Choleris et al., 2011), although the brain sites of this action are still unknown. The hippocampus has been implicated in the early processing of memories of a socially induced food preference, and dopaminergic neurons in the ventral tegmental area have terminations to several limbic system structures, including the hippocampus. Hence, this experiment sought to establish a role for the D1 family of dopamine receptors in the CA1 region of the dorsal hippocampus. To do this, in an on-going study, we are microinfusing the dopamine D1-type receptor antagonist, SCH23390 (1, 2, 4, and 6 µg/mouse), into the hippocampus of adult male and female CD-1 mice 15 min prior to a 30 min social interaction during which mice acquire a food preference from a conspecific. Our examination of the interplay between the hippocampus and dopamine during the initial processing and subsequent storage of socially-acquired information will elucidate one likely brain site of dopaminergic involvement in social learning. In view of the known regulation of the dopaminergic system by the sex hormones and the participation of estrogens in social learning, our investigation will also highlight possible sex differences in social learning and dopaminergic action in male and female responses to environmental stimuli of a social nature. Supported by NSERC.

3-F-161 Inducible rescue of NMDA receptor deficiency and characterization of schizophrenia endophenotypes

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The etiology of schizophrenia remains unknown, however there is strong scientific support that the pathophysiology of the disease includes a dysfunction of glutamate neurotransmission during the development of the brain. While the pathology of schizophrenia may arise during brain development, symptoms of schizophrenia do not emerge until adulthood. This raises the question of whether therapeutic interventions in adults can reverse symptoms that arise from neurodevelopmental deficits. To address this question, we have generated a mutant mouse line (NR1-IR) capable of inducible rescue of NMDA receptor deficiency (deficit in glutamate signalling). The mouse model is based on a previously developed mutation, the NR1 knockdown (NR1-KD), which expresses low levels of NMDA receptors due to an intronic insertion (Mohn et al., 1999). In the new model, the intronic insertion is loxP flanked, allowing reversal of the mutation and restoration of gene function by Cre recombinase. Taking advantage of tamoxifen-inducible activity of Cre recombinase, we will remove the foreign DNA at two key timepoints; 6 weeks or 12 weeks, ultimately restoring expression of the Grin1 gene. The NR1-IR mouse model recapitulates the previously described behaviours of the NR1-KD mouse prior to treatment with tamoxifen. Once treated with tamoxifen, we will assess the extent of phenotype reversal by examining biochemical, cellular and behavioural phenotypes. This work helps us better understand the plasticity of the brain, and can also indicate pivotal developmental periods for treatment and intervention.

3-F-162 Prelimbic Neuron Coding of Concrete and Abstract Stimulus Features in Trace Eyeblink Conditioning

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After learning single neurons in the prelimbic region of the medial prefrontal cortex (PrL) gradually develop memory selective firing patterns believed to represent its emerging role in the modulation of memory expression (Takehara-Nishiuchi and McNaughton, 2008). Here, we examined how PrL neurons encode concrete (i.e., specific stimulus attributes) and abstract (i.e. relationship between stimuli) features of memory episodes. We recorded single unit activity in the PrL while rats received two epochs of trace eyeblink conditioning in which the conditioned stimulus (CS) was presented either alone (first 20 trials) or paired with eyelid shock (US, next 80 trials) using two different CS modalities (light and tone). 60% of neurons showed sustained firing rate changes during the interval between the CS and US. Some neurons differentiated their response depending on CS-US contingency (20%; association-selective neurons) whereas others did not (45%; non-selective neurons). Only a small proportion of these neurons differentiated their response based on the CS modality (4% and 5% for association- and non-selective neurons, respectively). Thus, PrL neurons appear to differentially encode memories mainly based on relationships between stimuli, but less on specific details of the stimulus. This suggests that the PrL may extract salient features from past experiences, the accumulation of which could result in schematic representations of relationships between stimuli/rules (Wallis et al., 2001; Rich and Shapiro, 2009).

3-F-163 Designing a More Clinically Relevant Exercise Paradigm

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Voluntary wheel running increases neurogenesis in the adult hippocampal dentate gyrus (DG). Neurogenesis is thought to be involved in neuronal plasticity and might help restore altered function due to neurodegenerative disorders and stroke. However, studies often provide animals with unlimited access to running wheels. Patients typically have time or physical limitations, so this paradigm lacks clinical relevance. We sought to design an exercise paradigm that would translate better to the clinic and investigate its effect on neurogenesis in the DG. Male Sprague-Dawley rats were randomly assigned to five groups: 4 hr (4HR), 8 hr (8HR) and 24 hr alternate day (AR) runners that were granted access to the running wheel every other day, 24 hr runners (UR) that had access to the running wheel every day and Sedentary (Sed) rats. Running took place for 2 weeks. On the first week, new cells were labelled with bromodeoxyuridine (BrdU, one injection/day, 50mg/kg, i.p.). BrdU-positive cells were quantified throughout the rostrocaudal extent of the granule cell layer of the DG. The AR and UR groups ran significantly more than the 4HR, 8HR, and Sed rats. There was no difference in the total distance ran over two weeks between the AR and UR groups. Surprisingly, AR rats showed significantly more BrdU positive cells than any other group. These findings suggest that moderate exercise can increase neurogenesis to a greater degree than extended bouts of exercise. Ongoing analysis will determine the phenotype of proliferating cells in the DG and define the most effective paradigm.

3-F-164 Functional connectivity of macaque prefrontal cortex cells reveals area 46 as one source of attentional control

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The flexible control of attention is achieved by functional interactions of cells within segregated areas in the prefrontal cortex (PFC). Previous studies suggest that cells within (i) the dorsal PFC (area 46) implement a top-down representation

that guides attention, (ii) the caudal PFC (area 8/9) serves to maintain attentional information over time and (iii) the anterior cingulate cortex (ACC, area 24) primarily monitoring activity in the PFC to adjust activity when task demands or rewards change. It is unknown how these three PFC subareas functionally interact during states of selective attention. We tested this question of functional connectivity by recording the spiking activity of >3000 pairs of cells from distinct PFC subdivisions in two macaques performing a selective attention task. We quantified the relative frequency and direction of area-specific interactions with shift-predictor corrected cross-correlations. We found that during states of selective attention, cells in area 46 exert widespread excitatory influences onto ACC (area 24) and caudal PFC. In contrast to this largely unidirectional excitation, we found significant bi-directional inhibition between cells in areas 46 and 24. Functionally specific, inter-areal interactions were not accounted for by mere distance effects between areas. These results provide direct evidence that area 46 cells are a major source of attentional top-down signals and suggest that ACC cells are continuously coupled with area 46, consistent with their putative monitoring function during goal-directed behavior.

3-F-165 Representational demands modulate involvement of perirhinal cortex in face processing

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The classic view holds that the medial temporal lobes (MTL) are dedicated to declarative memory functioning. Recent evidence, however, suggests that perirhinal cortex (PrC), an anterior MTL structure, may also support perceptual discrimination when complex conjunctions of features must be represented. Studies with non-human primates have also revealed a face patch in the anterior collateral sulcus with preferential responses to face stimuli. Here, we investigated the representational demands that influence PrC involvement in different types of face judgments using fMRI. Holding stimulus complexity constant, we independently manipulated the nature of the task and the orientation of the stimuli (through inversion). Aspects of right PrC showed increased responses in a forced-choice recognition-memory and a perceptual-oddity task, as compared to a task that probed detection of an isolated face feature. Effects of stimulus orientation in right PrC were observed when the recognition-memory condition for upright faces was compared with all other experimental conditions, including recognition-memory for inverted faces- a result that relates to a role of PrC in object unitization. Notably, both effects in right PrC paralleled activity in broader networks that included the right fusiform gyrus and the amygdala, regions frequently implicated in face processing. These findings add to a growing body of evidence suggesting that the functional role of specific MTL structures may be best understood in terms of the representations that are required by the task and the stimuli at hand.

3-F-166 The role of striatal acetylcholine in cognition: Behavioural phenotyping of mice deficient for vesicular acetylcholine transporter (VAChT).

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Much of the work investigating the role of acetylcholine in cognition has focused on neurons within the basal forebrain cholinergic system. In addition , however, there is an independent cholinergic system in the striatum. The role of striatal cholinergic neurons in cognition and behaviour remains unclear. Here we present data from a genetic mouse model that has disrupted cholinergic transmission in the striatum due to localized knockout of the Vesicular Acetylcholine Transporter (VAChT). Previous research with these mice revealed normal performance on a 1-hour

delay object recognition test. The goal of the present research is to further characterize striatal cholinergic activity by assessing mice on a cognitive battery. Additionally, the question of whether there are sex differences in striatal cholinergic activity was addressed by testing males and females. Results from social and object recognition paradigms have revealed specific impairment in mice deficient for striatal acetylcholine when tested at 5-minute or 15-minute retention delays. The impairment was more severe in female mice than males. This impairment was not present in 3-hour delay tasks in either sex. Furthermore, the knockout mice displayed normal performance on an object location paradigm at all delays. The results of this study suggest that striatal cholinergic neurons are involved in short term processing of object and social recognition. Future work, including studies with touchscreen-based operant tasks, will continue to assess the cognitive profile of these striatal VAChT knockout mice.

3-F-167 The neural basis of strategic decision-making: An fMRI approach

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During competitive social interactions, one's chosen actions and their associated outcomes change dynamically based on the actions of other agents. This often requires that one avoid exploitation from opponents by employing the use of mixed-strategies; choosing among available actions unpredictably and stochastically. Mathematical frameworks to predict optimal strategies in social situations are outlined by game theory, however, discrepancies exist between these optimal strategies and how people actually behave.Functional MRI was used to investigate the neural processes related to mixed-strategy decision-making. A colour-based version of Matching Pennies was played against a dynamic computer opponent that exploited biases in players' response patterns. Participants selected one of two different coloured visual targets, and were rewarded if their selection matched that of the opponent. Results were contrasted with a control task that matched the strategic task in terms of sensory input, choice direction, and reward rate. Therefore, any differences in brain response patterns should highlight strategic-related processes.Results demonstrate that strategic decision-making is associated with activation of a highly distributed network, including bilateral dorsolateral prefrontal cortex, parietal cortex, anterior cingulate gyrus, the right superior temporal sulcus, and the insular cortex, in addition to known occulomotor circuitry. We propose that the observed activation represents the core elements of a distributed functional network underlying strategic forms of decision-making

3-F-168 Rapid enhancing effects of estrogens on learning are mediated by ERα in the hippocampus

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Estrogens non-genomically affect neural electrophysiology and dendritic spine density. Recently, we showed low doses of systemic 17β-estradiol improved social recognition, object recognition and object placement learning in ovariectomized mice within 40min of treatment (Phan et al., 2012. Neuropsychopharm, 37:2299). This appears to be mediated through estrogen receptor (ER) α, since ERα agonist PPT also improved performance on all 3 paradigms, whereas ERβ agonist DPN only improved object placement learning (Phan et al., 2011. Endocrinology, 152:1492). Furthermore, 17β-estradiol and PPT increased CA1 hippocampal dendritic spine density, whereas DPN had no effect or decreased spine density. Thus, the hippocampus may be involved in mediating the rapid effects of estradiol on learning. We infused 0.5µL (per side) of vehicle, 17β-estradiol (25, 50, 100nM), PPT (50, 100, 150nM) or DPN (50, 100, 150nM), into the hippocampus of CD1 ovariectomized female mice, 15min prior to testing social recognition, object recognition and object placement performance in home cage.

Paradigms were completed at 40min post-infusion to target estrogens' non-genomic effects. We found that intrahippocampal delivery of 50nM 17β-estradiol and of 100 and 150nM PPT improved performance on all 3 learning paradigms, while intrahippocampal 100nM DPN improved only object placement learning. Therefore, the hippocampus is able to mediate the non-genomic enhancement of estrogens on learning through activation of ERα. Funded by NSERC.

3-F-169 Effects of sex and duration of social pairing on neurogenesis in zebra finches (Taeniopygia guttata).

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One model system in which adult neurogenesis has been studied is the songbird, such as the zebra finch (Taeniopygia guttata). Zebra finch males produce two types of song directed and undirected. Social context mediates which of these he performs: directed song is sung only during courtship of a female. In this study, we examined the relationship between social context, behaviour, and adult neurogenesis in the zebra finch by assigning birds to same-sex or opposite-sex pairs and administering the cell birth marker bromodeoxyuridine (BrdU), then counting the number of labeled cells in the subventricular zone (SVZ), a zone of cell birth in the avian brain. Three different sacrifice timelines were used to investigate which stage of neurogenesis (proliferation and survival) was affected and whether length of pairing played a role. We also analyzed video recordings of pairs to quantify song and other behaviours. Males tended to have more BrdU cells than females, and there were more cells in the SVZ when measured 1 day after BrdU injection than after 10 days; this may be attributable to cell migration or reduced survival. We also compare results of both used two protocols for labelling BrdU neurons.

3-F-170 EEG and molecular responses to sleep deprivation in Neuroligin 1 knockout mice

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Background: Sleep loss is known to affect cortical synchrony of neuronal firing and synaptic function. Neuroligin 1 (Nlgn1) is a synaptic adhesion molecule required for normal synaptic function and involved in neuronal plasticity. The aim of this study was to assess the role of Neuroligin 1 in the response to acute sleep loss. Methodology: Male mice carrying a Nlgn1 mutation (knockout n=12, heterozygotes n=16) or wild-type littermates (WT n=10) were studied. 1) Mice were implanted with EEG and EMG electrodes. Then, EEG was continuously recorded for 4 days including a 6h sleep deprivation (SD). Vigilance states were identified and compared between genotypes. 2) One week after, the same mice were sacrificed either after a 6h SD or at the same time under undisturbed conditions followed by brain sampling. Total RNA was extracted and mRNA expression level of genes consistently showing a response to SD (Homer 1a, Bdnf, Per2, Fos, Arc) was measured by qPCR. Results: 1) Nlgn1 KO mice are more difficult to keep awake during SD but the efficiency of SD in the three groups was identical. In the active period following SD, Nlgn1 KO do not show a decrease of Wakefulness duration and a increase in Non-Rapid Eye Movement Sleep as observed in WT and heterozygous mice. 2) SD increased the expression of all target genes similarly in WT and Nlgn1 KO mice. In addition, forebrain Fos expression was lower in Nlgn1 KO mice than in WT. Conclusion: Our study highlights the role of Neuroligin 1 in the response to elevated need for sleep, as revealed by the altered sleep rebound in Nlgn1 KO mice

3-F-171 Acute effect of aerobic exercise on cognitive function by exercise duration & time

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A single bout of aerobic exercise has been associated with improvements to cognitive function among young and older adults. The optimal duration of acute exercise and the time course of post-exercise cognitive effects are unknown. Objectives were to examine the relationship between exercise duration and cognitive function and to examine the time-course of cognitive changes post-exercise. Nine young adults completed a baseline (which included a predictive VO2max test) a 20 and a 40 min. exercise session on a cycle ergometer. At each session, participants performed 3 modified flanker tests separated by 10 min., coupled with electroencephalography (EEG). Exercise was completed at 60% predicted VO2 max followed by the flanker. Repeated measures ANOVA was used to analyze accuracy and reaction time from the flanker and P3 amplitude and latency from EEG event-related potentials. Reaction time had a significant 2-way interaction for congruency*time (F=18.15, p=<0.0001) and a 3-way interaction for congruency*session*time (F=50.93, p=<0.0001). Flanker accuracy had a significant 2-way interaction for congruency*time (F=6.09, p = 0.01) and 3-way interaction for congruency*session*time (F=11.69, p=<0.0001). Analysis of P3 amplitude and latency revealed significant main effects for region only (F=3.50, p=0.03 and F=13.59, p=<0.0001 respectively). Flanker task performance was influenced by a complex interaction between exercise, time post-exercise and congruency. In this study, there were no evident cortical changes due to exercise.

3-F-172 Mapping the functional connectome of the adult-born DG granule cells at the cellular scale

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Adult-generated granule cells (aDGCs) are integrated into pre-existing hippocampal circuits, gradually establishing functional input and output connections. Using transgenic and retroviral approaches here we track the development of aDGC functional and anatomical connectivity. Injection of a retrovirus expressing GFP into the DG allowed us to visualize the output connections of aDGCs in naïve mice. By four -but not six- weeks, aDGC mossy fibers showed significantly more filopodia and en passant boutons -specialized presynaptic cellular compartments contacting GABAergic cells- than developmentally-generated cells, suggesting that aDGCs transiently develop extensive anatomical connections with inhibitory CA3. This transient increase of connectivity suggests that these two populations of cells may show learning-dependent functional coupling during a specific time window. To test this, we developed a novel approach to map the functional coupling of multiple cell populations during the formation of a memory trace. Using the immediate early gene fos as neuronal activity marker combined with transgene expression and immunofluorescence we found that fos expression was tightly correlated between 4w aDGCs and GAD CA3 cells across subjects, indicating that activity of 4w -but not 6w- aDGCs and CA3 inhibitory cells is tightly coupled. Taken together these results suggest that aDGCs establish strong anatomical and functional connections with inhibitory CA3 cells early on during their development and this synaptic integration may have a significant impact on hippocampal processes.

3-F-173 Differential Effects of Aging on the Memory for Spatial and Temporal Relations

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The hippocampus critically supports memory for the relations among objects (Konkel et al., 2008), including spatial and temporal relations. Older adults often show relational memory deficits;

presumably due to disproportionate atrophy in the hippocampus (Naveh-Benjamin, 2000). However, whereas there are many aging studies on spatial memory, there are fewer studies on temporal memory, and even fewer on the interaction between them. The present study examined age-related differences in, and interactions between, spatial and temporal memory. Young and old adults performed a short-delay recognition memory task while eye movements (EM) were recorded. On each trial, participants viewed a set of three novel objects, individually presented in a particular temporal order and spatial configuration. After a 2 s delay, the same three objects were presented again, but either their relative spatial locations, temporal order, or both were changed for half the trials. Participants were instructed to detect changes to either the spatial or temporal relations. Young adults demonstrated EM evidence for spatial and temporal memory, whereas old adults only demonstrated EM evidence for spatial memory and only when instructed to focus on spatial relations. Recognition accuracy for spatial relations was disrupted by changes in temporal relations; an effect that was stronger in old adults than young adults. These findings show that aging is accompanied by a disproportionate decline in temporal versus spatial memory, suggesting that the hippocampus does not support memory for all relations equally.

3-F-174 An Analysis of Cortico-Cortical Connections during Memory Consolidation

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Memories for events may initially be encoded in hippocampal-cortical networks. However, as these memories age they may become predominantly dependent upon cortical regions for their retrieval. Changes in the strength of cortico-cortical connections are thought to underlie this transformation, allowing the memory to be expressed independently of the hippocampus at remote time-points. Cortico-cortical connections (measured as the change in the proportion of active, c-Fos labelled cells that anatomically connect from one region to another) from the visual association area 2 (V2) to the anterior cingulate cortex (Cg-a) increase in mice as contextual fear memories age. However, the quantity of c-Fos positive cells in the V2 does not linearly increase through time. Instead, there is peak activity in V2 during recall of 7d old contextual fear memories, while 28d old memories exhibit similar activity compared to 1d old memories. In order to determine whether 28d old memory networks are qualitatively different from 1d old memory networks, V2 lesions were performed on mice at various time-points after being subjected to contextual fear conditioning. Lesions of V2 at 1d, 7d, and 14d did not impair recall of fear memories; however, a lesion at 28d significantly impaired recall. Thus, over time memory networks in V2 are refined; a non-critical network consisting of large number of cells is pruned into a qualitatively different network containing fewer, though necessary, cells.

3-F-175 Changes in patterns of regional brain activation accompanying memory transformation

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It is widely believed that the hippocampus is required for formation (consolidation) of new episodic memories but its continued role in memory retention and retrieval is less clear. Regions within prefrontal cortex show increased activation during retrieval of remote memories, suggesting a time-dependent reorganization of brain regions involved in memory consolidation. It is less clear how the nature of the memory (vividness, richness of detail) changes as it becomes represented in a diffuse brain network. The Transformation Hypothesis of consolidation proposes that episodic memory is initially highly-detailed and dependent upon hippocampus, but over time, that memory loses perceptual richness,

retaining the general elements of the memory as it becomes represented in a diffuse cortical network. However, the hippocampus is thought to always be required for retrieval of richly detailed elements of the memory. The goal of the present study is to assess how the passage of time affects the quality and neural representation of episodic memory. We will use fMRI to visualize changing brain activation patterns in humans recalling film clips of events to analyze qualitative changes in richness of details of their remembered events at different timepoints. By dissociating brain regions that normally process different forms of an episodic memory, we can apply these activation patterns to aging and patients with dementia to determine how different activation patterns may reflect differences in memory transformation, and may even account for observations of preserved forms of memory.

3-F-176 Arc catFISH visualization of neuronal ensemble changes in the piriform cortex following odor discrimination learning in rats

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Pattern completion and separation are unique processes underlying sensory perception and memory. In the piriform cortex, theoretical models and extracellular multi-unit recordings have demonstrated neuronal ensemble changes resembling pattern completion and separation during odor discrimination. In this study, we explore a direct visualization of neuronal ensemble changes following odor discrimination learning in rats. The cellular compartment analysis of temporal activity by fluorescence in situ hybridization (catFISH) technique allows us to examine the expression of an immediate early gene, Arc, in two cellular compartments following two behavioral episodes. Hence patterns of neuronal ensembles activated by two odors or two episodes of the same odor can be compared. Preliminary data suggest that pyramidal neurons express Arc in an input specific manner - the same cell was more likely to transcribe Arc following repeated exposure to the same odor (peppermint) than cells in animals that were exposed to two odors (peppermint and vanillin). We are currently investigating whether and how pyramidal cell ensembles are modified by odor learning. Adult rats were trained in a go/no-go odor discrimination task with two odors - peppermint as the reward odor, vanillin as the control. After successful odor discrimination is acquired, animals were re-exposed to peppermint or vanillin in order to examine Arc expression in pyramidal cells following these odors. Further analysis will determine whether pyramidal cell ensembles are modified by odor discrimination learning.

3-F-177 Local cell assemblies in macaque prefrontal and anterior cingulate cortex detect and distinguish error types

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Detection of errors or unexpected outcomes is critical for learning and sequential behavioral adjustments. Neurons associated with errors signaling (ES) have most prominently been found in anterior cingulate cortex (ACC) and lateral prefrontal cortex (lPFC). However, it is currently unclear whether these ES neurons distinguish different error types. We recorded single neuron activities across the fronto-cingulate cortex (FCC) of two rhesus monkeys during a selective attention task, and examined whether ES neurons distinguished errors committed: (i) during sustained selective visua lattention (indicative of motivational lapses), (ii) around the time when salient distractors occurred (indicative of faulty attentional capture), or (iii) during a perceptual choice about the rotation direction of a stimulus. Among >800 recorded neurons, 13% showed significant ES firing rate modulation for motivational lapses, 8% indicated attentional failure, and 9% for wrong perceptual choices. Motivational ES were anatomically clustered within local regions in lPFC and ACC, but attentional and choice ES predominated within the

ACC. These findings reveal that separable subsets of cells within FCC respond to separable error types, suggesting that ES neurons encode information regarding error causation. These findings support the unique role of the lPFC/ACC in learning and improving choices and attentional deployment in trials subsequent to errors.

3-F-178 Neuroanatomical, neurofunctional and neurobehavioral sequelae of mild hypoxia following cardiac arrest: Is the hippocampal truism true?

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Cardiac arrest (CA) is the most common cause of hypoxia-ischemic neural damage. Severe CA-related cognitive impairment is well described, but brief ischemia patients often lack neurological follow-up. Brain tissue can survive 4-5 minutes without oxygen, but there is great individual variability. The selective vulnerability hypothesis posits that the hippocampus is more susceptible to hypoxia, but it is primarily based on anecdotal reports and animal models. The goal of the project was to examine the hypoxic damage to the hippocampus and other neural structures after brief global ischemia and relate that to patients' performance on neuropsychological memory assessments. We predicted that the variability in neurological outcome in patients who have suffered from brief hypoxia will be directly related to their hippocampal volume. CA survivors who were discharged from hospital with diagnosis of 'good neurological outcome' were scanned and tested on a battery of neuropsychological tests and patients with Myocardial Infarctions (MI) served as controls. Hippocampal volumes were manually traced on T1 MRI images. Preliminary data showed significant cognitive deficits primarily in the memory domain. There were also significantly reduced mean hippocampal volumes bilaterally and larger variability in CA survivors compared with controls. There were also strong correlations between hippocampal volumes and standardized measures of memory. Overall, these data support the hypothesis of hippocampal damage and associated cognitive dysfunction that occurs even after a brief hypoxic episode.

3-F-179 Effects of TMS over dorsolateral prefrontal cortex on multiple-visual object memory across fixation and saccades

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Constructing a unified visual scene involves integrating information across multiple fixations, known as transsaccadic integration (Irwin, Cognitive Psychol. 1996). Short-term visual memory and transsaccadic memory appear to share a capacity of 3-4 items. Prime et al. showed that transcranial magnetic stimulation (TMS) over right posterior parietal cortex (PPC, J. Neurosci. 2008) and right frontal eye fields (FEF, Cereb. Cortex 2010) during a saccade, reduces this memory capacity. Here, we used a similar paradigm to investigate the role of dorsolateral prefrontal cortex (DLPFC), involved in spatial memory, in transsaccadic memory of multiple objects. We hypothesized a less saccade-specific role than PPC and FEF. Participants were required to indicate whether a target amongst distracters rotated clockwise or counterclockwise after a 750ms memory interval. This interval contained either fixation only, or a saccade with randomized metrics. Single-pulse TMS was delivered over DLPFC and control site CZ during the memory period. Performance in the fixation task was significantly reduced in a time-dependent manner during TMS over left and right DLPFC. Performance in the saccade task exhibited facilitation with TMS, with a significant increase in performance for right DLPFC stimulation. TMS over CZ had no significant effect in either condition. The variable suppression and facilitation effects seen here with TMS, may suggest that the DLPFC plays a

less saccade-specific role in transsaccadic memory and harnesses cognitive control aspects that are not yet well understood.

3-F-180 An urgency/vigor signal governs speed-accuracy trade-offs in both decision-making and movement execution

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We test the hypothesis that a unified mechanism for reward rate maximization determines the speed-accuracy trade-off during both decision-making and movement execution. Two monkeys were trained to perform a reaching decision task in which sensory evidence continuously evolves during the time course of a trial. In different blocks, the temporal properties of the task were varied to induce adjustments of monkeys' speed-accuracy trade-off. Monkeys' accuracy decreased as a function of decision time, suggesting that decisions were based on the product of the sensory information and a growing urgency signal. Consistent with the idea that the same urgency signal could influence execution, both monkeys executed shorter arm movements after longer decisions and during blocks in which they favoured speed over accuracy. Moreover, the velocity of saccades increased over the time course of a trial, and was higher in the fast blocks. Many premotor and primary motor cortex neurons reflected the evolution of the sensory information and reached a peak at decision time. This activity was amplified when monkeys emphasized speed over accuracy. Other neurons, which show a velocity-related burst of activity after decision time, showed larger bursts after longer decisions, as if also influenced by the same urgency signal. Our results suggest that the eye and arm systems receive an urgency signal that serves as a global source of vigor for decisions as well as movement execution. Support: CIHR (MOP-102662), CFI, FRSQ, and EJLB Foundation, FYSSEN and GRSNC fellowships to DT, GRSNC fellowship to JT

3-F-181 Systemic inflammation increases the hypnotic effects of etomidate and isoflurane but not ketamine

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Systemic inflammation can dramatically increase the sensitivity of patients to the neurodepressive properties of general anesthetics for reasons that remain poorly understood. Mechanistically, general anesthetics produce loss of consciousness (hypnosis) principally by increasing the activity of γ-aminobutyric acid type A receptors (GABAARs). We recently showed that systemic inflammation increases the surface expression of extrasynaptic GABAARs (Cell Reports, 2012), suggesting that inflammation increases the number of target receptors for anesthetics. Here, we tested the hypothesis that inflammation increases the efficacy of anesthetics that increase GABAAR function (etomidate and isoflurane). In contrast, inflammation should not alter the efficacy of anesthetics that do not target GABAARs, such as ketamine, a NMDA receptor antagonist. To induce acute systemic inflammation, adult male mice (3-4 months old) were treated with the endotoxin lipopolysaccharide (LPS) (125 µg/kg, i.p.) 3 h prior to the administration of etomidate (14 mg/kg, i.p.), isoflurane (1.0%), or ketamine (63 mg/kg, i.p.). Latency to loss of righting reflex (LORR) was assessed, which serves as a surrogate measure for hypnosis. LPS increased the efficacy of etomidate and isoflurane to cause a LORR ($P = 0.002$, $P = 0.021$, respectively). In contrast, LPS did not alter ketamine-mediated LORR ($P = 0.688$). These results suggest that systemic inflammation increases the hypnotic effects of anesthetics by enhancing the activity of GABAARs.

3-F-182 Contribution of noise correlations to neuronal population coding of saccade direction in macaque area 8a

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Previous single-unit electrophysiological studies have demonstrated that neurons in area 8a of macaques are involved in the planning and execution of saccadic eye movements. Here, we implanted 96-channels multielectrode arrays in the area 8a of two macaques and recorded single and multiunit activity while they performed a visually guided saccade task to one out of four presented targets. Simultaneous neuronal spiking activity aligned to the initiation of the saccade was inputted into a support vector machine (SVM) algorithm to optimize a model predicting to which quadrant of the screen the monkey would saccade. Including all neurons, the model achieved 67% accuracy in predicting saccade end point. Including only neurons with significant spatial tuning increased the model accuracy to 94%. In order to assess the effect of the simultaneity of the neuronal activity on model performance, we destroyed simultaneity by shuffling trials' identity within experimental conditions, which concomitantly abolishes noise correlations. Surprisingly, noise-correlations-free activity yielded significantly better prediction accuracy both when all neurons were included (+9%) and when only spatially tuned neurons were selected (+4%). These preliminary results suggest that neuronal population activity in the macaque area 8a can be decoded to predict stereotyped saccade end point with high accuracy, and that noise correlations have a slight detrimental effect on population decoding using a SVM classifier.

3-F-183 delta-GABAA receptors promote memory and neurogenesis in the dentate gyrus

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Objective: gamma-Aminobutyric acid type A receptors that contain the delta subunit (dGABAARs) are highly expressed in the dentate gyrus (DG), where they regulate neuronal activity. The DG is critically involved in memory and also exhibits significant neurogenesis, but the role of dGABAARs in these processes is poorly understood. Accordingly, we sought to determine the role of dGABAARs in learning and neurogenesis. Methods: Learning and neurogenesis were studied in wild-type (WT) mice and transgenic mice that lacked dGABAARs (Gabrd-/-). To pharmacologically increase dGABAAR activity, mice were treated with the dGABAAR-preferring agonist 4,5,6,7-tetrahydroisoxazolo(5,4-c)pyridin-3-ol (THIP). Behaviour was measured in recognition memory, contextual discrimination and fear extinction assays. Neurogenesis was studied by measuring the proliferation, survival, migration, maturation and dendritic complexity of adult-born neurons in the DG. Results: Gabrd-/- mice exhibited impaired recognition memory, contextual discrimination and fear extinction relative to WT mice. Neurogenesis was disrupted in Gabrd-/- mice as the migration, maturation and dendritic development of adult-born neurons was impaired. Long-term treatment with THIP facilitated learning and neurogenesis in WT but not Gabrd-/- mice. Interpretation: dGABAARs promote learning and neurogenesis, and can be pharmacologically targeted to enhance these processes.

3-F-184 GSK-3Beta inhibition more potently blocks acquisition than expression of amphetamine-produced conditioned place preference in rats

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Behavioural sensitization and incentive learning are mediated by dopamine (DA). The signaling molecule glycogen synthase kinase-3β (GSK-3β), activated downstream of DA D2-like receptors, affects DA-mediated behaviours. For example, inhibition of GSK-3β attenuates locomotor sensitization to psychomotor stimulant drugs. Few studies have examined the effects of GSK-3β inhibition in incentive learning paradigms. We examined the effects of GSK-3β inhibition on incentive learning

produced by amphetamine (1.5 mg/kg) in the conditioned place preference (CPP) paradigm. The selective GSK-3 inhibitor SB 216763 was administered intraperitoneally to male Wistar rats at doses of 1.0, 2.0, and 2.5 mg/kg during the acquisition or expression phase. Due to studies more strongly implicating signaling molecules in acquisition rather than expression of learning, we hypothesized a block of acquisition of CPP at doses that fail to block expression of CPP. Results supported this hypothesis: the 1.0 mg/kg dose of SB 216763 failed to block either acquisition or expression of CPP; the 2.0 mg/kg dose blocked acquisition but not expression of CPP; and the 2.5 mg/kg dose blocked both acquisition and expression of CPP. These results indicate that inhibiting GSK-3β may attenuate incentive learning differentially in acquisition versus expression of conditioning. (Funded by NSERC)

3-F-185 Test Environment Pre-exposure Mediates Catalepsy Sensitization Response: Possible Role of Dopamine D1-Like Receptors

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Novel environmental stimuli have been shown to activate the dopamine (DA) system and habituation to these conditions reduces such activation. Decreases in brain DA lead to catalepsy, quantified by the time a rat remains with its forepaws resting on a suspended horizontal bar. Low doses of the DA D2 receptor-preferring antagonist haloperidol (0.25 mg/kg, i.p.) repeatedly injected in a particular environment lead to gradual day-to-day increases in catalepsy (sensitization). Previously, we showed that pre-exposing rats to the testing environment subsequently produced a greater catalepsy sensitization response across testing days. We hypothesized that under conditions where DA release is low, as in habituated animals, haloperidol will be more effective at further reducing DA transmission such that it shifts the catalepsy sensitization curve to the left. The current project examined whether post-trial treatment with the D1-like receptor antagonist SCH 23390 (0.05 mg/kg, i.p.), 30-min following each pre-exposure session would block the shift in the sensitization curve. Rats were pre-exposed to the catalepsy test environment (context A) or a different environment (context B) for 6 days (5-min/day), and were then subjected to a catalepsy sensitization test over the next 13 days. Results show that post-trial treatment with SCH 23390 during pre-exposure in context A blocked the subsequent shift in the catalepsy sensitization curve. Our results show that D1-like receptors play an important role in memory consolidation of previously experienced environmental stimuli. (Funded by NSERC)

3-F-186 Circuit tagging by CREB facilitates the formation of new fear memories

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Recent experience can influence the formation of subsequent memories. We investigated if formation or recall of an amygdala-dependent fear memory can influence the subsequent formation of a second distinct fear memory. In mice that were trained in two separate auditory fear conditioning tasks with two distinct tones, we observed the second memory was enhanced if the first training session occurred 6h, but not 24h, before the second. Intriguingly, formation of the second memory was also enhanced if animals recalled the first memory 6h before training for the second memory. The enhancement of the second memory correlated with increased overlap between the proportion of lateral amygdala (LA) neurons activated during each memory task. This suggests that some temporally limited cellular and network changes induced by formation of a fear memory "primed" these neurons to be preferentially involved in encoding a second memory. We hypothesized that these changes may involve the transcription factor CREB as we observed that CREB activity peaks 6h after fear conditioning and returns to baseline after 24h. Accordingly, increasing CREB

levels in a subset of LA neurons using viral-mediated gene delivery mimicked the effects of previous training on memory formation and inactivation of those same neurons before training or testing using engineered hM4D receptors prevented memory formation and expression, respectively. Collectively, these results indicate that CREB activity associated with one memory can transiently "tag" a circuit in the LA, thereby facilitating subsequent new learning.

3-F-187 Amphetamine differentially alters behaviour of high, intermediate, and low impulsive rats on the five-choice serial reaction time task and the conditioned reinforcement test

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Environmental stimuli can acquire motivational salience and act as conditioned reinforcers (CRs). Drugs of abuse may enhance these properties, contributing to the development of addiction. As abnormally high levels of impulsivity are associated with addiction, this enhancement may be stronger in high impulsive subjects. To determine the relationship between impulsivity and salience of a CR, male Long Evans rats were trained on the 5-choice serial reaction time task (5CSRTT)--a widely-used test of motor impulsivity--and separated into low (LI), intermediate (II), and high (HI) impulsive groups. Animals were then tested on a CR paradigm, in which thirsty rats press a lever to receive a stimulus previously paired with water reward (a CR). The effects of an acute amphetamine injection were assessed on each task. On the 5CSRTT, amphetamine increased impulsivity in all groups; however, HI rats were more sensitive to lower amphetamine doses. LI rats initially responded more for the CR compared to both HI and II rats. Although amphetamine increased CR responding in all groups, LI rats demonstrated the greatest increase. The CR response was then extinguished by removing the stimulus presentation. Amphetamine increased responding on the inactive-CR lever, but this effect was blunted in HI rats. Therefore, the ability of amphetamine to enhance the salience of a CR appears to be greater in LI rats. As dopamine (DA) largely contributes to amphetamine's effects on these tasks, microdialysis will be used to measure DA release in the nucleus accumbens following an amphetamine injection.

3-F-188 Luman/CREB3 and Luman-Recruitment Factor LRF/CREBRF regulate the HPA axis through the glucocorticoid receptor signaling pathway

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Under stress, the activation of Hypothalamic-Pituitary-Adrenal gland (HPA) axis leads to the production of glucocorticoids, which in turn regulate this pathway through negative feedback. Alterations in the glucocorticoid receptor (GR) result in altered HPA axis activity are known to lead to signs of depression, anxiety and maternal behavior abnormalities. Luman and its binding protein and regulator, LRF, are two transcription factors involved in the unfolded protein response in response to stress in the endoplasmic reticulum. Recently we have found that both LRF and Luman gene knockout mice displayed similar phenotypes in the maternal instinct deficiency. The elevated GR activity in LRF null mice is believed to be responsible for the suppression of prolactin synthesis and the associated maternal behavioral phenotype. Here we report that Luman also repressed GR activity in a cell-based reporter assay. Further behavioral analysis showed that LRF null mice appeared anxiolytic, with less sense of fear, which is similar to the observation of the GR overexpression (YGR) mice. To investigate this phenotype further, the dexamethasone (Dex) suppression test (for depression), and the Dex suppression with corticotropin releasing hormone (CRH) challenge (adrenal insufficiency) were performed in virgin LRF null and wildtype littermates. Corticosterone levels were also compared in both null and wildtype littermates postpartum as well as in virgin controls. Our data suggest that Luman and LRF work in concert in regulating the HPA stress signaling through the repression of GR activity.

G – Novel Methods and Technology Development

3-G-189 Internalization Contributes To Desensitization Of Camp Inhibition By Delta Opioid Receptor Ligands

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Recent studies have linked the duration of different DOR responses to distinct internalization patterns, suggesting that ligand-specific endocytic trafficking could constitute a viable strategy for developing better tolerated longer lasting DOR analgesics. Here we have correlated the magnitude and kinetics of a typical biochemical response (inhibition of cAMP production) with the internalization profile of different DOR agonists. In HEK293 cells the rank order of maximal internalization was: DPDPE=Deltorphin=SNC-80=Met-Enk>>>mcpTIPP>SB235863=morphine. Maximal inhibition of cAMP production at 5 min stimulation was the same among all ligands, except for DPDPE and morphine that were respectively higher and lower than the rest. Rank order of EC50 values was similar to internalization: DPDPE=Deltorphin>SNC-80=Met-Enk=mcpTIPP>SB235863>morphine. Despite these similarities the duration of the cyclase response was different. Indeed, cAMP inhibition was transient for DPDPE and Met-ENK, reaching pre-stimulation values within 15 min (decay of response t ½ : 4.4 min for DPDE; 4.1 min for Met-ENK). Response by the other ligands did not decay completely, remaining at 40-45% inhibition for mcpTIPP and SB235863 and at 20-25% for SNC-80, Delt and morphine. Internalization blockade by dynamin inhibitor dynasore enhanced and prolonged cAMP inhibition by all ligands, but the effect was larger for internalizing agonists. Among the latter, the effect of dynasore on signalling was proportional to its ability to inhibit sequestration. Taken together these data indicate that internalization contributes to rapid desensitization of DOR signalling but this parameter is not a universal predictor of the duration of the cAMP response.

3-G-190 In search of babies: Using Mechanical Turk to examine infant stimulus preferences

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Rich stimuli, like movie segments, have been used to study distributed patterns of neural activity while participants remain engaged for an extended period of time. While our understanding of different neural networks in the adult brain has grown substantially, our understanding of the development of these networks remains limited. One potential limitation of conducting these studies in infants is identifying a set of stimuli they find engaging. However, gathering the appropriate data is often met with a number of important challenges, (e.g., recruiting cooperative infants). The aim of my study is to find a set of highly engaging stimuli using Mechanical Turk, a crowd-sourcing platform run by Amazon, to efficiently and affordably recruit infant participants to complete online behavioral tasks. During a pilot experiment, participants uploaded webcam pictures of their infants looking left, right and center. We were able to recruit 16 infants between 2-11 months, who produced high quality data within 72 hours, suggesting that Mechanical Turk could be an effective resource for recruiting infant participants. Next, we will use a modified head turn preference procedure adapted for online use to determine infants' preference for various types of musical stimuli. Participants' webcams and computer microphones will be used to collect both audio and visual data, which in turn will be outsourced to other Mechanical Turk workers for scoring. We expect infants to prefer high pitches, increased tempos, and metric rhythms.

3-G-191 Magneto-articulography for the Assessment of Speech Kinematics (MASK): An MEG-compatible motion-tracking device for measuring brain activity during speech tasks

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We describe a novel technology, Magneto-articulography for the Assessment of Speech Kinematics (MASK), which allows for concurrent measurement of brain activity and oromotor movement using Magnetoencephalography (MEG), a brain imaging technique that measures weak magnetic fields produced by neural activity. Speech production involves the precise coordination of many muscles that direct articulator movements. How the brain orchestrates these intricate movements of speech is relatively unknown. Commercial motion tracking systems such as the electromagnetic articulograph (EMA) are the preferred method for studying articulator movements, but cannot be used together with MEG due to magnetic interference. The newly developed MASK system overcomes this barrier by utilizing small tracking coils attached to articulators, as in EMA, but tracked with the MEG sensors, allowing for concurrent recording of brain and oromotor activity. The objective of the current study was to validate the accuracy of motion tracking by MASK when compared to EMA, and to demonstrate its feasibility for use in individuals with and without speech disorders. Participants performed identical speech and non-speech oral tasks in both MASK and EMA systems. Articulator movements tracked by MASK were compared to reference data established by EMA. Initial results showed that MASK was able to robustly extract speech movement data that exhibited the same parametric features as found in EMA. Once MASK is validated more extensively, it can be utilized to inform new treatments and therapies for speech disorders.

3-G-192 Genetically encoded calcium indicators: a comparative study of GCaMPs and GECOs using two-photon excitation fluorescence microscopy in hippocampal neurons

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Imaging calcium transients associated with neuronal activity has yielded important insights into neural physiology. Genetically encoded calcium indicators (GECI) offer conspicuous potential advantages for this purpose, including exquisite cellular and even subcellular targeting. While the catalog of available GECIs is steadily growing, many newly developed sensors that appear promising in vitro or in model cells perform less usefully when expressed in neurons. We have tested the two-photon performance of GECIs from the GCaMP family (Nakai et al., 2001) and the GECO family (Zhao et al., 2011). We used two-photon excitation fluorescence microscopy to compare the somatic Ca2 transients reported by GCaMP3, GCaMP-3-H, GECO1.0, 1.1, 1.2, B-GECO, R-GECO, CAR-GECO, and O-GECO. After optimizing excitation wavelength, responses to increasing numbers of action potentials evoked by depolarization were monitored from CA1 pyramidal neurons in rat organotypic hippocampal slices. Some GECIs, but not others, were able to detect single action potentials with high reliability. Kinetics of all responses were too slow to follow individual action potentials at high frequencies, but signal amplitudes with some GECIs were linearly related to number of spikes over a useful range. Nakai J, Ohkura M & Imoto K (2001) Nature Biotechnology 19, 137-141. Zhao Y, Araki S, Wu J, Teramoto T, Chang Y-F, Nakano M, Abdelfattah AS, Fujiwara M, Ishihara T, Nagai T & Campbell RE (2011) Science 333, 1888-1891.

3-G-193 Optogenetics in cortical and subcortical structures of non-human primates

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Optogenetics is a novel technique that allows researchers to modulate neuronal activity using

exogenously expressed light-sensitive ion channels. This technique has been increasingly relied upon to depolarize or hyperpolarize neurons of defined populations with millisecond-scale induction and reversibility. Despite its methodological advantages, few research groups have successfully applied optogenetics in primates. We injected the excitatory opsin channelrhodopsin-2 (ChR2) and the inhibitory opsin eNpHR3.0 in cortical and subcortical regions of two Macaca fasciculari. RNA plasmids containing the promoter human thymocyte differentiation antigen-1, ChR2 or eNpHR3.0, and yellow fluorescent protein were carried within a lentivirus vector (Lenti-hThy-1-ChR2(H134R)-eYFP or Lenti-hThy-1-eNpHR3.0-eYFP). Injections of ChR2 in the frontal eye field were visually guided using landmarks of the cortical surface anatomy. Approximately 6 months after injection, we measured single unit activity in this region in the awake monkey using a single electrode coupled to an optic fiber and a 473 nm laser. These neurons exhibited up to 70-fold increases in firing rate during light stimulation compared to the pre-stimulation period, albeit at a longer than expected latency (~100 ms after light onset). Subcortical injections of ChR2 and eNpHR3.0 in the medial septum were MRI-guided using a stereotax free neuronavigation system. Preliminary histological analyses show opsin expression in astrocytes and neurons. Further analyses of the proportion and genetic identity of transfected cells are ongoing.

3-G-194 Fitting dynamical models of activity to data over surface of mouse cortex

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We fit a simplified mathematical model of neural dynamics to very high-resolution data on neural activity levels over the surface of one hemisphere of mouse cortex, recorded using voltage-sensitive dyes under light anesthesia. The model includes both intrinsic local dynamics and inter-regional communication. We find that intrinsic dynamics seems to account for only a modest fraction of this delta rhythm activity, and that spreading activation and activation from distal cortical regions seem to account for a similar fraction. We identify many specific connections that appear statistically significant.

3-G-195 Lipid nanoparticle delivery of siRNA to silence neuronal gene expression in the brain

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Manipulation of gene expression in the brain is fundamental to understanding the function of proteins involved in neuronal processes. Current strategies for manipulating neuronal gene expression in vivo are costly, time consuming and often inefficient. Here we show a method for delivery of siRNA in lipid nanoparticles (LNPs) that provides a highly effective method for silencing neuronal gene expression in the brain. We show that neurons accumulate these LNPs in an apolipoprotein E dependent fashion, resulting in very efficient uptake both in cell culture and in vivo, with little apparent toxicity. When the LNPs contain siRNA, selective knockdown of the target gene is achieved. In vivo delivery of siRNA against GRIN1 (encoding GluN1 subunit of the NMDA receptor) results in functional disruption of NMDAR currents. Therefore LNP delivery of siRNA rapidly manipulates expression of proteins involved in neuronal processes in vivo, possibly enabling development of gene therapies for neurological disorders.

3-G-196 A chemical genetic approach to projection field mapping of central hunger circuits

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Cell type specific tools for manipulating neuronal activity have advanced our ability to assess the connectivity and function of neural circuits.

However, the functional dissection of circuits is often complicated by the fact that a given neuronal population gives rise multiple axon projections, innervating a diverse variety of downstream effectors. Behavior evoked by activating a single population of neurons may thus be mediated by any or all of these downstream target regions. In the following study, we identify a chemical genetic approach to produce spatially restricted, cell type specific silencing of an axonal projection field. We find that the engineered version of the human muscarinic receptor 4 (hM4D) inhibits synaptic transmission at excitatory and inhibitory synapses in the cortex and hypothalamus. Cell type specific co-expression of channelrhodopsin and hM4D in hypothalamic AGRP neurons allows us to evoke a robust feeding behavior that can then be inhibited with the application of the hM4D ligand, clozapine-N-oxide (CNO) to a specific projection field, the paraventricular hypothalamic nucleus. Thus silencing synaptic projections with hM4D allows us to functionally dissect a complex feeding circuit by removing synaptic transmission to individual projection fields.

IBRO – International Brain Research Organization

3-IBRO-197 Assessment of Post Operative pain using the FLACC Model in Children in Kenya

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Background: Pain in children is an area insufficiently understood. It is however accepted that the nociceptive system is developed before birth and that children may actually have an exaggerated response to pain. Pain management in children is however often inadequate is mainly due to inadequate assessment. The FLACC model has been recommended for use in children between 2 months and 7 years of age. Its use has however not been reported in children post operatively especially post neurological surgery. Methodology: The study involved children under the age of 7 years operated on over a 2 year period at the Kenyatta National Hospital. The children were evaluated 24 hours before posterior fossa craniotomy for intracranial neoplasms and at 24 & 48 hours post operation. The assessment of pain was carried out by two physicians simultaneously but independently and recorded using the FLACC model. Parents also scored pain using a visual analog scale at the same time. Results: Majority of patients were aged 2-4 years. 324 results were recorded from 126 children over the study duration. Inter-observer variability in scoring was minimal and statistically not significant. This was for each category (Spearman p=0.64-0.82, P<0.001) and total score (Spearman p=0.73, P<0.001). There was correlation of the FLACC score and the visual analog score (P<0.001). Conclusion: The FLACC model of pain assessment is a valid tool that can be used in post neurosurgical pain assessment in children. Its results are consistent, repeatable and correlate to other pain scores.

3-IBRO-198 Phα1β, a peptide from the venom of the spider Phoneutria nigriventer, shows antinociceptive effects after continuous infusion in a neuropathic pain model in rats

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Neuropathic pain is a severe painful pathology that is difficult to treat. One option for its management is the continuous intrathecal (i.t.) infusion of ziconotide (the Conus magnus peptide ω - Conotoxin MVIIA), which, in addition to being efficacious, produces serious adverse effects at analgesic doses. Single i.t. administration of Phα1β, a peptide purified from the venom of the spider Phoneutria nigriventer, possesses antinociceptive effects with a greater therapeutic window than ziconotide in rodents. We also investigated the antinociceptive and toxic effects of Phα1β after single or continuous i.t. infusion in a rat model of

neuropathic pain. We observed that chronic constriction injury of the sciatic nerve but not sham surgery caused intense (reduction of approximately 2.5 times in mechanical withdrawal threshold) and persistent (up to 14 days) nociception in rats. The single i.t. injection of Phα1β (30 or 100 pmol/site) abolished neuropathic nociception from 1 to 6 hours after administration, without showing detectable side effects. Similarly, the continuous infusion of Phα1β (60 pmol/μL/h for 7 days) was also able to reverse nerve injury-induced nociception from 1 to 7 days (full inhibition from days 3 to 7) but did not cause either behavioral side effects or histopathological changes in the central nervous system. Thus, we have shown for the first time that the continuous i.t. delivery of Phα1β produces analgesia disconnected from toxicity in a relevant model of neuropathic pain, indicating that it is an effective and safe drug with a great potential to treat pain.

3-IBRO-199 Combined Evaluation Of Brainstem Reflexes In Patients With Early Amyotrophic Lateral Sclerosis

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Introduction: Brainstem reflexes (BSR) have been used to document upper motor neuron (UMN) involvement in amyotrophic lateral sclerosis (ALS). We hypothesized that combined evaluation of BSR is more informative than a separate analysis of each in early ALS. Objectives: To determine whether a battery of BSR discriminates ALS patients from controls better than the independent evaluation of reflexes. Methods: Masseter inhibitory (MIR), masseter direct (MR), blink reflex (BR) and BR habituation, were evaluated in 11 definitive spinal ALS patients (<1 year of evolution) and 15 age-matched healthy controls, following published guidelines (masseter reflexes through chin taps; BR electrically, its habituation in a paired stimulation paradigm). To evaluate discriminating capabilities of BSR between control and patient groups, stepwise discriminant analysis were performed in two ways: 1-including variables from only one type of reflex in each model; and 2-including variables from all reflexes in a combined model. Results: MR and MIR model misclassified 23,08% of subjects (Wilks-Lambda p<.0603). With BR model, misclassification reached 33,33% (Wilks-Lambda p<.0475). In BR habituation model the 30% was wrongly classified (Wilks-Lambda p<0,1667). The combined model, which included MR amplitude, MIR duration, BR R2 duration and R2 habituation (ISI=1 s), was the most efficient, providing accurate classification of 94,46% of subjects(Wilks-Lambda p<.0007), only one control incorrectly allocated. Conclusion: The combined use of BSR allows better discrimination of early ALS patients.

3-IBRO-200 The implication of opioid receptor gene polymorphisms on pain perception

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Morphinic receptors are located on the membrane of neuronal cells. The doses of morphine needed for pain relief vary between individuals. Some of this variation is explained by variable bioavailability and differences in intensities of pain stimuli. However, lack of a direct relationship between serum concentrations of morphine and patient characteristics suggests that interindividual variability may be related to an interaction between morphine and opioid receptors In this study, we focused on four polymorphisms in Mu opioid receptor gene (MOR1) and three in the Kappa opioid receptor gene (OPRK1), and their association to morphine doses needed to decrease the pain intensities in tunisian cancerous patients We have collected 100 blood samples from cancerous patients under morphine treatment at differents doses. DNA extraction was achieved for those patients. By PCR, we have screened DNA for an INDEL of 830pb in the promoter region of the OPRK1, 45,9% of our patients have the deletion. By SnaPShot technique we have screened 40 DNA for 6 SNP in MOR1 and OPRK1 gene. All have

heterozygocy for the Mu 17C>T, and only one is heterozygot for Kappa 15 C>T Study is in progress to achieve the screening of all our DNA sample for the seven polymorphisms and to perform statistical analysis for our population.

3-IBRO-201 Spinal cord injury pain in South Africa

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Spinal cord injury (SCI) is devastating, affecting many South African's. Although loss of motor & autonomic function is often considered to be the principle effect of SCI, pain is also a major sequel of this devastating injury (Trunks, 1986; Siddall et al., 1999). Indeed, previous studies reported that 69% of SCI patients experience pain, & nearly one-third of these patients described their pain as severe and disabling (Siddall et al., 1999). Although these figures give an indication of the prevalence of pain following SCI, historically the nature of the pain is not well depicted. This description of SCI-related pain creates a challenge to patients, clinicans and researchers in the aftermath of SCI (Cruz-Almedia et al., 2005) To date research concerning this injury in South Africa has investigated the etiology, incidence of cervical injuries in rugby players & epidemiology in Johannesburg. However no study has reported on SCI pain in South Africa which is a major impediment in the aftermath of such injury The purpose of this study was to measure three aspects of pain measurement in a South African sample of acute traumatic SCI patients viz. 1. Classification of SCI-related pain; 2. Pain perception & 3. pain interference. The following assessment tools were used: 1. Pain intensity:0-10 numerical pain rating scale, McGill Pain Questionnaire (MPQ) 2. Pain quality: MPQ, Neuropathic Pain Scale 3. Pain interference: Modified Brief Pain Inventory-Interfence Scale 4. Pain Catastropizing Scale Preliminary results will be discussed

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