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Abstract Booklet

Poster Sessions:
Poster Session A: Thursday September 21, 1:40-3:15PM, 6:00-7:00PM
Poster Session B: Thursday September 21, 7:00-8:00PM, Friday September 22, 1:25-3:15PM

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Session A: Thursday 1:40-3:15pm, 6:00-7:00pm

A1) MiR-218 in the Prefrontal Cortex mediates Resilience to Chronic Stress

Angelica Torres-Berrio, Dominique Nouel, Santiago Cuesta, Gustavo Turecki, Eric J. Nestler, Cecilia Flores

Introduction: We recently identified miR-218 as repressor of the guidance cue receptor gene DCC (Deleted in colorectal cancer). Indeed, low miR-218, but exaggerated DCC, expression in the prefrontal cortex (PFC) are consistent traits of human depression, and stress-induced depression-like behaviors in mice. Remarkably, miR-218 can be measured in blood, suggesting its potential role as novel biomarker of vulnerability to depression.

Methods: Here we used C57BL/6 mice, viral-mediated gene transfer, and quantitative-PCR to assess whether (1) direct manipulation of miR-218 in the PFC determines resilience or susceptibility to chronic social defeat stress (CSDS), (2) miR-218 expression in blood correlates with depression-like behaviors, and (3) variations in blood expression of miR-218 depends on changes in levels of miR-218 in PFC. Results: We report that miR-218 is expressed by pyramidal neurons in the mouse PFC. We then find that overexpression of miR-218 selectively in PFC pyramidal neurons prior to CSDS promotes resilience to stress by reducing social avoidance. Conversely, blocking the function of miR-218 in the PFC before a single social defeat exposure induces susceptibility to stress. We also find that expression of miR-218 in blood correlates with depression-like behaviors and that susceptible, but not control or resilient, mice exhibit low levels of miR-218 in blood. Most importantly, we demonstrate that changes in blood expression of miR-218 resemble the ones observed in the PFC.

Conclusion: Our results reveal that miR-218 in the PFC functions as a molecular switch that determines resilience or susceptibility to chronic stress. Remarkably, stress-induced variations in PFC levels of miR-218 can be readily detected in blood. We are currently assessing whether miR-218 levels in both PFC and blood change in response to antidepressant treatment. We propose that blood expression of miR-218 might function as potential biomarker of vulnerability to stress and predict the outcome of therapeutic or pharmacological interventions.

A2) In vivo fiber photometry reveals signature of future stress susceptibility in nucleus accumbens

Jessie Muir* [1], Zachary S. Lorsch [3], Charu Ramakrishnan [2], Karl Deisseroth [2], Eric J. Nestler [3], Erin S. Calipari [3], & Rosemary C. Bagot [1,3] 1. Department of Psychology, McGill University, Montreal, QC, Canada 2. Department of Bioengineering, Stanford University, CA, USA 3. Fishberg Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Alterations in nucleus accumbens (NAc) activity have been linked to the pathophysiology of depression. Mice that exhibit depressive-like symptoms after chronic social defeat stress (CSDS) show distinct changes in NAc activity. However, the pre-existing individual differences that make certain mice resilient and others susceptible to stress are yet to be described. We hypothesized that individual differences in NAc activity present before exposure to stress may associate with future stress susceptibility. Using fiber photometry, we recorded activity in NAc D1- and D2- medium spiny neurons (MSN) in awake behaving mice. We report that, prior to stress, mice that later become resilient have higher D1 ? MSN activity than mice that later become susceptible, an effect observed both in baseline neuronal activity and during social interaction. We suggest that reduced D1-MSN activity before defeat may be a predisposing factor for stress susceptibility. We also observed differences in D2- MSN activity temporally correlated with behavior, pointing to an additional role for D2-MSN in susceptibility to stress. These findings suggest a possible underlying mechanism of stress-induced susceptibility and offer the potential to predict at-risk individuals prior to encountering stress.

A3) Small Non-coding RNAs in Major Depression and Antidepressant Response

Rixing Lin*, Juan Pablo Lopez, Laura Fiori, Raoul Belzeaux, Cristiana Cruceanu, Jean-Francois Theroux, CANBIND working group, Jane Foster, Sidney Kennedy, and Gustavo Turecki

Background: Major depressive disorder (MDD) affects between 6.4%-10.1% of the population. Despite its prevalence and considerable burden, our understanding of the pathophysiology remains unclear. Antidepressants are the most common treatment for MDD, yet on average 30%-40% of patients experience an inadequate response to treatment after several attempts. Thus, there is a great need to identify biomarkers associated with MDD and which predict response to antidepressant treatment. Recent discoveries have pointed towards small non-coding RNAs (sncRNA) as feasible biomarkers. While the majority of studies have focused on microRNA, evidence suggests that small nucleolar RNAs (snoRNAs), which are involved in alternative splicing and chemical modifications of RNAs, may also act as novel biomarkers for antidepressant response.

Methods: A cohort (Lundbeck samples) of 258 depressed patients were treated either with the antidepressant duloxetine (N=124) or placebo (N=134) for a period of 8 weeks. Blood samples were collected at baseline (T0) and 8 weeks into treatment (T8), and RNA sequencing was performed to detect expression changes of sncRNAs. At time T8, patients were grouped into responders to duloxetine and non-responders of duloxetine. Group separation was determined based on a 50% reduction of MADRS score from time T0 to T8. The expression of the top snoRNAs, from responders of duloxetine, showing significant differences in their expression profiles from T0 to T8 was assessed in neural progenitor cells (NPCs) treated with duloxetine for 2 weeks using qRT-PCR. Results: Small RNA sequencing revealed 22 snoRNAs showing significant increase in expression in responders of duloxetine treatment. Validation experiments using a sub-group of the small-RNA sequencing cohort showed SNORD17 and SNORD99 to be significantly up-regulated. These results were also observed in NPCs treated with duloxetine.

Conclusion: This is the first study profiling snoRNAs in MDD and antidepressant response, and these preliminary results suggest that the candidate snoRNAs may be good mediator biomarkers of antidepressant response.

A4) Resting State Connectivity of Striatum and Midbrain Nuclei: Relation to Impulsivity, Sensation-Seeking and Body Weight

Rachel J Sharkey*, Josiane Bourque Kevin Larcher, Yu Zhang, Ayca Altinkaya, Abbas Sadikot, Alan C. Evans, Hugh Garavan, Marco Leyton, Jean R. Seguin, Robert Pihl, Patricia Conrod, Alain Dagher

High levels of trait impulsivity (IMP) and sensation-seeking (SS) are common features of adolescence and believed to be related to the ongoing development of fronto-subcortical circuitry. However, while these traits increase within subjects during adolescence, they also vary between subjects. Since high levels of IMP and SS are associated with an increased risk for obesity, this study examined correlations between the connectivity of nuclei in the basal ganglia and dopaminergic midbrain with body weight, and measures of IMP and SS in a population of young adolescents. Resting state fMRI data were collected for 116 children between the ages of 12 and 14. Connectivity with regions of interest in the left and right sub-thalamic nucleus (STN), ventral striatum (VS), ventral tegmental area (VTA) and substantia nigra (SN), was correlated with body mass index (Z-Scored for age) and IMP and SS scores from the Substance Use Risk Profile Scale. IMP was positively correlated with the connectivity between the left VS and the ventromedial prefrontal cortex, and the left STN and temporal and parietal regions. SS was negatively correlated with the connectivity between the left and right VTA and the anterior cingulate cortex and temporoparietal-junction. BMI Z-Score for age was positively correlated with the connectivity between the right SN and left STN and the entorhinal cortex, the left and right STN and the parahippocampal gyrus, and the left VTA and the cerebellum. This may reflect differences in networks regulating decision-making and food choices associated with these traits.

A5) Netrin-1 functions as a long-range chemoattractant

Celina Cheung*, Karen Lai Wing Sun, Stephanie Harris, Timothy E Kennedy

Netrin-1 is a secreted guidance protein proposed to function as both a short-range and long-range chemotropic cue. Previous studies have provided evidence that secreted netrin-1 acts as a long-range chemoattractant, forming a gradient that directs embryonic spinal commissural axons to the ventral midline of the neural tube. Ex vivo studies using explants have demonstrated that an ectopic source of cells secreting netrin-1 can orchestrate growth cone turning through the developing neuroepithelium from up to 250 um away. In contrast, recent papers have claimed that netrin-1 functions solely as a short-range permissive cue, that there is no gradient, and that netrin-1 does not exert an instructive function that directs axon extension. Here, using validated monoclonal antibodies, we show that netrin-1 protein is distributed in the embryonic neuroepithelium many cell diameters away from its source, which is the defining characteristic of a long-range cue. We visualize and quantify the distribution of netrin-1 in vivo, revealing a gradient in the embryonic spinal cord as the first commissural axons are extending to the ventral midline. Through genetic manipulation of levels of netrin-1 expression, we demonstrate that the distribution of netrin-1 protein is crucial for appropriate commissural axon guidance. Our findings demonstrate that a gradient of secreted netrin-1 functions as a long-range chemoattractant that directs embryonic commissural axon extension in the embryonic spinal cord.

A6) DNA methylation: an epigenetic predictive biomarker of antidepressant response

Chelsey Ju*, Laura M. Fiori, Jean Francois Theroux, Jane Foster, Sidney Kennedy, CAN-BIND working group, Gustavo Turecki

Major depressive disorder (MDD) is a severe diagnosis recognized as the leading cause of global disability. Antidepressant therapy (ADT) is the standardized first-line treatment, but an estimated 60% of patients fail to respond initially, and 20-30% do not respond after multiple interventions. Identifying a biomarker molecule for ADT response would promote the evidence-based clinical guidelines. MDD has a heterogeneous phenotype, and demonstrated by various groups to be a factor of an affected individual's environment. DNA methylation, particularly at CpG dinucleotide sites, is an epigenetic mark that serves as a suitable candidate for biomarker studies given its stability and accuracy, even when retrieved from indirect, surrogate tissue such as peripheral blood. Differentially methylated positions (DMPs) between ADT responders and non-responders of the Canadian Biomarker Integration Network in Depression (CAN-BIND) cohort were assessed to evaluate their suitability as predictive biomarkers for ADT response. Peripheral blood samples were obtained from 206 MDD patients and 101 healthy controls (HCs). MDD patients were subjected to 8 weeks of escitalopram ADT. At week 0 (pre-ADT), and week 8 (post-ADT), MDD patients received Montgomery-Asberg Depression Rating Scale (MADRS) scores for symptom severity. A patient was considered a responder (RES) if they had a ? 50% MADRS score decrease, and a non-responder (NRES) otherwise. Genome-wide methylation analysis was conducted using Illumina?s EPIC microarray platform. Array data was pre-processed, and analyzed with the ChAMP Bioconductor package in R. Differential methylation analysis was performed between i. HCs and MDD patients and ii. ADT RES and NRES. Furthermore, week 0 genome wide expression data was acquired from the same cohort using Illumina?s HT-12 Beadchip platform. DMPs found between RES and NRES that overlap with differential gene expression findings will be subject to targeted validation using bisulfite amplicon sequencing. 16, 582 DMPs were found between MDD patients and HCs, and 1, 655 DMPs were found between RES and NRES ($p<0.05$, FDR=0.1). 1,087 genes were found to be differentially expressed between RES and NRES ($p <0.05$). After overlap analysis, 57 genes were found to have both differential expression methylation. The top 5 DMPs selected based on greatest absolute methylation change will be further validated using targeted bisulfite sequencing.

A7) Diurnal variation of performance, vigilance, and somnolence throughout a complete rotating work roster in police officers on patrol

Fernando Gonzales*, Philippe Boudreau, Diane B. Boivin

Shift work is associated with circadian and sleep-wake disturbances. Shift workers, such as police officers, have a greater risk of sleepiness, impaired vigilance, and performance during work time due to circadian misalignment. The aim of this study was to document subjective alertness, somnolence, and psychomotor performance throughout a complete work roster in police officers working rotating shifts.

A total of 25 municipal police officers from Quebec (17 men, 8 women) aged 31.3±4.5 years (mean ± SD) were enrolled in a 35-day field study. Their rotating schedule comprised 9- or 12-hour day (0700-1600 or 0700-1900), evening (1500-2400), and night (2230-0730 or 1900-0700) shifts, alternating with rest days. During this period, they filled out the Karolinska Sleepiness Scale (KSS) and a visual analog scale (VAS) 5x/day to measure subjective sleepiness and vigilance, respectively. A 5-minute Psychomotor Vigilance Task (PVT) was also filled out at the beginning and end of their shifts. The diurnal variation of sleepiness, vigilance, median reaction time (RT), mean reaction speed (RS), and minor lapses (RT ≥ 500 ms) was analyzed using a nonlinear mixed model.

A significant 24-h variation was present for all the variables including median RT, mean RS, vigilance, and sleepiness ($p \leq 0.001$) with the fitted lowest performance between at 06:06±00:56h (mean ± SD) and the highest at 18:06±00:30h.

This study has demonstrated that circadian phase affects performance in rotating shift workers. The circadian nadir in the early morning suggests that, as a group, the circadian system of police officers remains adjusted to a day-oriented schedule independent of the shift worked. The results of this work have practical implications in terms of safety and productivity at work, as it identified critical times of reduced performance, namely at the start of day shifts and end of night shifts.

A8) Duration Dependency of Monocular Deprivation Induced Visual Plasticity

Seung Hyun Min*, Alex Baldwin, Alexandre Reynaud, Robert F. Hess

Short-term monocular deprivation has been recently shown to temporarily increase the sensitivity of the patched eye through neuroplastic changes in 4C- beta layer at the primary visual cortex. Several studies have patched participants for 2.5 hours arbitrarily. This project explores the duration-dependence of this deprivation-induced plasticity phenomenon to question the validity of patching for 2.5 hours. Three patching durations were tested in nine subjects: 1-, 2- and 3-hours. A translucent eyepatch was employed on subjects' dominant eyes during the patching sessions. A session included two rounds of baseline testing of interocular eye balance, patching, and post-patching tests, which are the abridged versions of the baseline testing. Each post-patching test occurred at 0, 3, 6, 12, 24, 48, 60 and 96 minutes after patching in order to track the effects over time. Every subject performed two sessions per condition. 1-hour patching produced small shifts in eye dominance. Larger shifts occurred from 2-hours patching, but 3-hours patching produced comparable effects to those measured after 2 hours of patching. These results show a saturation of the patching effect beyond 2-hours patching. Hence, we believe that 2-hours patching duration is the optimal duration for eye dominance changes induced by monocular deprivation.

A9) The impact of depressed mood and alcohol in risky driving

Nevicia F. Case*, Derek Albert, & Thomas G. Brown

Human factors, such as unsafe driving, are responsible for the majority of road traffic crashes worldwide. Mood, low doses of alcohol even within the legal limit, and poor executive functioning may contribute to a higher prevalence of unsafe driving. Little is presently known about the role of impaired executive function in the link between mood and unsafe driving. The proposed study is a randomised, double-blinded, placebo-controlled, between-subjects study which seeks to elucidate the cognitive influence of depressed mood on unsafe driving in a virtual-reality simulator. The study hypothesises that: (1) the frequency of the decision to drive while under the influence of alcohol, impairment in driving performance (i.e., lateral lane position), and risky driving (i.e., speed variability) in participants with both depressed mood and alcohol > participants with alcohol only > participants with depressed mood only > participants with neither depressed mood nor alcohol; and (2) executive function mediates the relationship between both predictors (depressed mood and alcohol) and both dependent variables (lateral lane position and speed variability). Participants will be healthy males age 20-24. After assessing baseline characteristics, two manipulations will occur: (1) either a depressed or a neutral mood induction and (2) consuming either an alcoholic or a placebo beverage. Self-reported and behavioural methods will measure the effects of the induced mood and alcohol on executive function and on unsafe driving during a simulator task. The results will advance scientific understanding of how cognition and affect interact to influence behaviour in driving, a task where performance is vital.

A10) Inhibitory synapse differentiation promoted by a novel neurexin2α -interacting cell adhesion molecule IgSF21

Naito Y*, Tanabe Y, Vasuta C, Lee A, Soumounou Y, Linhoff M. W & Takahashi H

Inhibitory synaptic inputs control neuronal excitability and the firing patterns of targeted neurons and further regulate brain circuit formation. The proper balance between excitatory and inhibitory synaptic inputs is crucial for maintaining normal brain functions. Accumulating evidence suggests that impaired development of central inhibitory synapses leads to neuropsychiatric disorders such as schizophrenia, autism spectrum disorders, and anxiety, highlighting the importance of our understanding of the molecular mechanisms of inhibitory synapse development. However, the molecular mechanism governing the development of GABAergic inhibitory synapses is poorly understood. Synapse development requires not only physical contact between axons and target neurons but also chemically-matched pre- and post-synaptic differentiation. Synapse organizers, synaptic adhesion molecules with the ability to induce synaptic differentiation, form trans-synaptic complex, called synapse organizing complexes. These complexes have been demonstrated as essential molecular signals for synapse development, represented by the neuroligin (NLG)-neurexin (NRX) complex. Although many synapse organizers induce excitatory or both excitatory and inhibitory synapses, there is only a few synapse organizer selectively inducing inhibitory synapse. Here, we report the identification of immunoglobulin superfamily member 21 (IgSF21) as a novel inhibitory synapse organizer that induce only inhibitory presynaptic differentiation. Through further proteomics screen, we isolated NRX2α as an IgSF21-interacting presynaptic organizer. Interestingly, IgSF21 selectively binds to NRX2a but not any other NRX isoforms and recruits NRX2α to presynaptic sites in a trans-synaptic interaction manner, which is essential for the synaptogenic activity of IgSF21. To characterize the physiological function of IgSF21 in the central nervous system, we comprehensively characterized IgSF21 mutant mice. We found that IgSF21 positively regulates inhibitory presynaptic organization and GABA-mediated synaptic transmission in the hippocampal CA1 pyramidal neurons and that IgSF21 is indispensable for normal sensorimotor gating. Together, our findings suggest that IgSF21 selectively organizes inhibitory synapses via its trans-synaptic interaction with axonal NRX2α and that this is essential for normal brain function.

A11) Added value of interleukin-1 blockade to hypothermia in neonatal encephalopathy due to inflammatory-sensitized hypoxia-ischemia: a preclinical study.

Chevin M*, Guiraut C, Sebire G.

Background: Neonatal encephalopathy (NE) and subsequent cerebral palsy (CP) resulting from hypoxia-ischemia (HI) or inflammatory-sensitized HI remain very prevalent and lead to significant mortality and morbidity. Few neuroprotective treatments are available against NE: they are limited to symptomatic care and hypothermia (HT), leaving about 50% of patients with neurological sequelae. We recently showed that HT fails to counteract the interleukin-1 (IL-1) system (Chevin et al., Int J Dev Neurosci, 2016), which play a key role in NE. This supports a potential neuroprotective benefit of IL-1 receptor antagonist (IL-1Ra) as targeted add-on therapy to HT.

Objective: We tested the added value of IL-1Ra administration to the neuroprotective effect of hypothermia (HT) in NE. Methods: We used a rat model of lipopolysaccharide (LPS)+HI-induced NE at postnatal (P) day 12. Inflammation was induced by injecting intraperitoneally (ip) 50 µg/kg of LPS from E.coli. Four hours (h) later, the right common carotid artery was ligated, then hypoxia was induced (8% O2, 1 h 30 min). Pups were submitted (or not) to HT (32° ± 0.5°C, 4 h). IL-1Ra (12.5 - 200 mg/kg q12 h) vs saline was injected ip from P12 to P14. Results: HT modestly alleviated brain injury. The neuroprotective effect of HT did not result from a down-regulation of the neuroinflammatory response mediated by IL-1β or TNF-α. IL-1Ra treatment (50 mg/kg) was well tolerated. It reduced core injuries and mortality of LPS+HI-exposed pups.

Conclusion: We demonstrate that IL-1Ra has an added value to the neuroprotective effect of HT in LPS+HI-induced NE. This project could open new therapeutic avenues to prevent CP.

A12) Optogenetic control of neuronal excitability in the entorhinal cortex: Are we going to control seizure as well?

Li-Yuan (Debby) Chen*, Maxime Levesque, Zahra Shiri, Sylvain Williams, and Massimo Avoli

Mesial temporal lobe epilepsy (MTLE) is one of the most refractory forms of epilepsy where seizures originate from limbic areas such as the hippocampus and the entorhinal cortex (EC). With up to one-third of patients not achieving effective seizure control, more effective therapeutic strategies are needed. Seizures can be classified into two categories based on their onset pattern: low-voltage, fast-onset (LVF) seizures and hypersynchronous-onset seizures (HYP). It has been suggested that the LVF seizure onset pattern results from $GABA_A$ -receptor signaling whereas the HYP onset pattern involves the activation of glutamatergic cells. Here, we tested this hypothesis by activating parvalbumin-positive or somatostatin-positive interneurons and calmodulin-dependent, protein kinase-positive, principal cells in the mouse EC in the *in vitro* 4-aminopyridine (4AP) model of epileptiform synchronization. We found that during 4AP application, both spontaneous seizure-like events and those induced by optogenetic activation of interneurons displayed LVF onset patterns. In contrast, seizures induced by the optogenetic activation of principal cells had HYP onset patterns. Next, we tested the efficacy of 1 Hz low frequency stimulation targeted to specific neuronal population in the EC to control seizures. We discovered that low frequency stimulation of both interneurons and principal cells are effective at reducing seizure frequency and duration in the 4AP model of epileptiform synchronization. We are now employing *in vivo* optogenetic procedure to show that stimulating interneurons in the EC could reduce the occurrence of spontaneous seizures in the pilocarpine model of MTLE. Our findings support further investigations to explore the use of targeted optogenetic stimulation as a therapeutic approach for the cure of MTLE.

Supported by CIHR MOP-130328 and the Savoy Foundation

A13) Caught in the act: In vivo 2-photon imaging evidence of phagocytosis of axons in the Xenopus laevis retinotectal circuit

Tony K.Y. Lim, Edward S. Ruthazer

There is accumulating evidence suggesting that microglia play an active role in synaptic pruning. However, while microglia are known to survey and contact synapses, real time evidence of microglia removing material from synapses has yet to be observed. Indeed, microglia may be arriving to clean up material from dead cells. Alternatively, pruned synapses may be ejected and microglia are simply passing by after the event has occurred to collect synaptic debris. The Xenopus laevis retinotectal circuit was used. Microglia were labelled by intraventricular injection with Alexa 594 conjugated to IB4-isolectin. To label RGC axons, RGCs were electroporated with eGFP plasmids, a mixture of 5% Alexa 488 dextran and 0.5% pHrodo green dextran, or plasmids expressing a pH-stable GFP. In long-term imaging studies, all analysis excluded any animals where axonal loss was detected. Morphologically, microglia in Xenopus larvae resemble the amoeboid microglia which have been described in neonatal rodents. Time lapse imaging demonstrated that microglia move at speeds between 1 to 10 Âµm/min. Contact between microglia and axons was observed. When axons were labelled with dextrans or with pH-stable GFP, microglia could be observed becoming more fluorescent after contact with labeled axons in real time. Long-term imaging studies over several days using pH-stable GFP also demonstrated a significant accumulation of green fluorescent material in microglia. This study provides evidence to support the hypothesis that microglia play active roles in axonal pruning.

A14) Metabolic Control of Macrophage-Mediated Myelin Phagocytosis: Implications for Multiple Sclerosis

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Background - The clearance of myelin debris by phagocytic monocyte-derived macrophages (MDMs) is essential for tissue repair in multiple sclerosis (MS). A selective defect in myelin phagocytosis but not in uptake of opsonized red blood cells by MS MDMs has been previously demonstrated (Natrajan 2015, Healy 2017). The metabolic state of MDMs, defined on the basis of oxidative phosphorylation (OXPHOS) and glycolysis, has been linked with the activation state of MDMs.

Objective - The aims of this study were to determine whether the metabolic activity of MDMs influences the rate of myelin phagocytosis, and then determine whether there was defect in metabolic activity of MS patient-derived MDMs. Methods - MDMs were prepared by isolating monocytes from whole venous blood samples derived from control donors and untreated MS patients (1 relapsing and 4 secondary progressive) and culturing these cells for 1 week in macrophage colony stimulating factor (M-CSF)-supplemented media. Myelin phagocytosis was measured using pHrodo-labelled myelin in a flow cytometry assay as described (Healy 2016). A Seahorse bioanalyzer was used to measure oxygen consumptions rates that predominantly reflect OXPHOS, and extracellular acidification rates that mainly reflect glycolysis.

Results - Both OXPHOS and glycolytic metabolism were upregulated in control donor MDMs following myelin uptake. Blocking OXPHOS by addition of the ATP synthase inhibitor oligomycin significantly reduced myelin phagocytosis. Blocking glycolysis by addition of the competitive inhibitor 2-deoxyglucose (2DG) did not reduce phagocytosis but did modulate subsequent cytokine production following phagocytosis. MS patient-derived MDMs showed significant deficits in both basal OXPHOS and glycolytic metabolism. Conclusion - Our data using control donor MDMs indicate a central role for OXPHOS in the control of myelin phagocytosis by healthy donor-derived MDMs. MDMs from MS patients display a deficit in both myelin phagocytosis and basal metabolic activity. The basis of this metabolic defect in MS MDMs remains to be defined.

A15) Performance of cognitive tasks promotes an automatic control of posture in young and older adults

Alexandra Potvin-Desrochers*, Natalie Richer, Deborah A. Jehu, Alan Chan, Yves Lajoie

Studies looking at the effects of performing of a concurrent cognitive task on postural control in young and older adults using spatial center-of-pressure measures and dynamical measures produced discordant results. Some found increased postural stability, while others found decreased stability. Improvements of postural stability have been suggested to be due to an automatization of postural control or to the use of an ankle stiffening strategy. It has been suggested that an automatic mode can be identified by an increase in entropy (i.e. more complex sway) and an increase in postural stability. Thus, the aim of this study was to compare the effects of cognitive tasks on postural control in healthy young adults and healthy older adults in order to confirm the postural control mode privileged in a dual-task paradigm using sample entropy. METHODS Twenty-one young adults and twenty-five older adults were asked to stand on a force platform while performing a cognitive task. Participants performed control standing as well as four cognitive tasks: two discrete and two continuous. The two discrete cognitive tasks consisted of a simple reaction time task and a go/no-go reaction time. For the simple reaction time task, participants were asked to verbally answer “top” as fast as possible when they heard high-pitched auditory stimuli. For the go/no-go reaction time task, participants were presented high-pitched and low-pitched stimuli. They had to respond “top” as fast as possible only when they heard high-pitched stimuli. For the first continuous cognitive tasks participants had to mentally resolve a series of simple mathematical operations. For the second continuous cognitive task, participants had to count the occurrence of a given digit in an auditory sequence of three-digit numbers. RESULTS In young adults, while mean velocity remained constant for all conditions, sway area and variability were significantly smaller in continuous tasks as opposed to control and discrete tasks. In older adults, sway area and variability in the anteroposterior direction decreased from control to discrete tasks and remained constant for continuous tasks. Increases in mean velocity and MPF were observed in older adults for the continuous tasks compared to control and discrete tasks. Finally, continuous tasks produced higher sample entropy than control and discrete tasks in both groups. CONCLUSION Results suggest that performing a concurrent cognitive task promotes the adoption of an automatic postural control in young adults and older adults as evidenced by an increased postural stability and postural sway complexity. Also, while adopting an automatic postural control, stability of older adults seemed to reach a plateau for continuous cognitive tasks, whereas young adults further increased their stability. Finally, results suggest that dynamical measures of sway may be more useful than spatial COP measures to interpret the postural strategy used.

A16) Susceptibility to depressive symptoms related to hippocampal memory engrams in an animal chronic stress model

Tianrui Zhang*, Vanessa Wong, Alice Wong, Tak Pan Wong

Apart from mood changes, depression has been associated with a biased memory for negative stimuli. Neuroimaging studies suggest this cognitive bias is related to the enhanced functioning of the hippocampus. We hypothesize that the facilitated formation of hippocampal engram cells, known as cellular substrates for memory, is related to the cognitive bias for negative stimuli in an animal model of depression. We employed a chronic social defeat model to examine the relationship between hippocampal engram cells and depression-related behaviours. The TetTag mouse model allows the tagging of activated neurons by a reporter gene LacZ. TetTag mice were stressed by social defeat, consisting of daily attacks by and co-housing with an aggressive mouse. Neurons activated in the first 2 days of social defeat were labeled by LacZ. After 8 total days of defeat stress, mice were separated into susceptible (exhibiting social avoidance) and resilient groups according to their social behaviour. Hippocampal engram cells are reactivated by an extra episode of social defeat to induce immediate early gene cFos expression. Neurons with both LacZ and cFos labeling represent engram cells. We found more LacZ labeled hippocampal CA1 neurons in susceptible mice compared with resilient and nonstressed control mice. Such group difference was still present the dorsal and ventral hippocampus were analyzed separately. This finding suggests there are inherent differences in hippocampal activation between susceptible and resilient mice before the onset of depressive symptoms in susceptible mice. Intriguingly, we also found significantly more engram cells in susceptible mice than other mouse groups in both the dorsal and ventral CA1 region in the hippocampus. No difference in LacZ labeled and engram cells was found in the dentate gyrus. Our findings suggest susceptible mice may have an enhanced hippocampal memory for social stress. Given that a hyperactive hippocampus may be related to rumination in depression, our findings that targeting hippocampal engram cells may be a novel therapy for depression.

A17) Spatial memory and learning require netrin-1 expression by neurons in the adult mammalian brain

*Edwin Wong, Stephen Glasgow, Lianne J Trigiani, Vladimir Rymar, Abbas Sadikot, Edith Hamel, Timothy E Kennedy

Netrin-1 was initially characterized as an axon guidance molecule that is essential for embryonic neural development. However, many neurons continue to express netrin-1 in the early post-natal and adult mammalian brain. Netrin-1 is highly enriched at synapses, and during synaptogenesis increases the number and strength of excitatory synapses made between glutamatergic cortical neurons. In the adult hippocampus, electrophysiological studies have provided evidence that activity dependent secretion of netrin-1 potentiates glutamatergic synapse function. Here, we address the impact of neuronal expression of netrin-1 in the adult brain on behaviour using memory and learning tasks. We show that adult mice with conditional deletion of netrin-1 from glutamatergic neurons in the forebrain exhibit impaired spatial memory, while working memory appears relatively unaffected. These findings provide evidence that netrin-1 expressed by neurons in the adult brain has an essential role in the regulation of excitatory synaptic plasticity that underlies spatial memory and learning.

A18) Effect of chronic salt intake on vasopressinergic magnocellular neurosecretory neurons in the supraoptic nucleus

David Levi* Masha Prager-Khoutorsky Charles W. Bourque

High dietary salt intake (HDSI) is a major risk factor for elevated blood pressure (hypertension) and is strongly correlated with the incidence of cardiovascular diseases and stroke. Increases in osmotic pressure due to increased plasma sodium levels are detected by osmosensitive neurons in the hypothalamus, called osmoreceptors. Osmoreceptors in the organum vasculosum laminae terminalis (OVLT) send an excitatory projection to the supraoptic nucleus (SON) and activate specialized magnocellular neurosecretory cells (MNCs), which are also intrinsically osmosensitive. These MNCs project to the neurohypophysis, from which they release vasopressin (VP) into the circulation. Recent studies, including those from our lab, have demonstrated that chronic exposure of rats to HDSI results in excessive activation of MNCs, leading to VP-mediated increases in blood pressure. Although this effect is associated with a reduction in the efficacy of inhibitory synaptic signaling by baroreceptors, it remains possible that a facilitation of osmoreceptor signaling can also contribute to this process. In this study, VP-eGFP Wistar rats were subjected to a 7-day salt-loading period in which their drinking water was replaced with 2% NaCl. Whole cell patch-clamp recordings of SON neurons were performed using an acute slice preparation that retains the OVLT?SON synaptic connectivity. Patched cells were fluorescently validated as VP-expressing using live fluorescent microscopy and then exposed to an acute hyperosmotic stimulus. Current clamp analysis revealed that the excitatory response of VP MNCs to hypertonicity was enhanced following HDSI. Ongoing voltage clamp analyses will examine if this effect is associated with an increase excitatory synaptic activity.

A19) Cholinergic enhancement of short-term patching in healthy adults

Yasha Sheynin*, Mira Chamoun, Alex Baldwin, Robert F Hess, Elvire Vaucher

Short-term monocular deprivation strengthens the patched eye's contribution to binocular combination, resulting in a temporary form of adult visual plasticity. Acetylcholine (ACh) has been shown to modulate visual plasticity and augment the magnitude and specificity of visual perceptual learning. In the present study, we investigate whether pharmacologically boosting levels of synaptic ACh with the cholinesterase inhibitor donepezil (5mg, administered 1.5 hours before patching) influences the strength and duration of short-term ocular dominance plasticity after monocular deprivation. We conducted a double-blind experiment where participants completed both a donepezil and placebo session on separate days. To measure the relative contributions of each eye to a cyclopean percept before and after 2 hours of patching, subjects were assessed using a well-known dichoptically-presented binocular phase combination task. Subjects completed this task before drug/placebo ingestion and again during five separate post-patching assessments that took place over the course of an hour. Our preliminary data suggest that cholinergic enhancement augments the effect of patching. Specifically, the patched eye contributed stronger to a binocular percept in the donepezil condition than in the placebo condition. This result implies that cholinergic potentiation may modulate adult ocular dominance plasticity.

A20) The highly selective mGluR2 positive allosteric modulator LY-487,379 alleviates L-DOPA-induced dyskinesia in the 6-OHDA-lesioned rat model of Parkinson's disease

Cynthia Kwan * Imane Frouni, Vaidehi Nafade, Dave Gagnon, Marie-Jose Wallman, Lamia Sid-Otmane Martin Parent, Andre Parent, Claude Rouillard, Adjia Hamadjida, Philippe Huot

The most effective treatment for Parkinson's disease (PD) is L-3,4-dihydroxyphenylalanine (L-DOPA) but with long-term use, the majority of patients develop motor complications such as dyskinesia. Dysregulation of glutamate homeostasis in the basal ganglia is implicated in the development of dyskinesia. Moreover, modulation of glutamatergic transmission with amantadine is an effective strategy to alleviate dyskinesia. Here, we hypothesized that activation of the metabotropic glutamate receptor 2 (mGluR2), represents a promising approach to reduce the severity of established, and prevent the development of, dyskinesia. Female Sprague-Dawley rats were rendered hemi-parkinsonian by administration of 6-hydroxydopamine (6-OHDA) into the medial forebrain bundle. Two sets of experiments were then conducted. In the first set, rats were primed with 10 mg/kg L-DOPA to produce stable axial, limbs and oro-lingual (ALO) abnormal involuntary movements (AIMs), after which they were administered L-DOPA in combination with the selective mGluR2 positive allosteric modulator LY-487,379 (vehicle, 0.1,1 and 10 mg/kg) and ALO AIMs severity was assessed. In the second set of experiments, rats were divided into 3 groups, LDOPA/vehicle, L-DOPA/LY-487,379 0.1 mg/kg, L-DOPA/LY-487,379 1 mg/kg, and primed daily for 21 days. After a 3-day washout period, they were all administered an acute challenge of L-DOPA and ALO AIMs severity was assessed. The effect of LY-487,379 on L-DOPA anti-parkinsonian action was determined by the cylinder test. In the acute challenges of LY-487,379, the 0.1 mg/kg dose, in combination with L-DOPA, significantly diminishes the severity of ALO AIMs, by 40% ($P < 0.05$), compared to L-DOPA alone. LY-487,379 at 0.1 mg/kg, started concurrently with L-DOPA, attenuates the duration and amplitude of the priming process leading to the development of dyskinesia, when compared to L-DOPA alone, by 60% and 59% ($P < 0.05$). Importantly, administration of LY-487,379 did not impair L-DOPA anti-parkinsonian action. These results suggest that selective mGluR2 activation is a promising and effective therapeutic strategy to reduce the severity, and attenuate the development, of L-DOPA-induced dyskinesia.

A21) Changes in the expression of myelin-related genes in the uncinate fasciculus of suicide completers following childhood abuse

John Kim, Meghan Shaw, Arnaud Tanti, Rachel Toope, Maria Antonietta Davoli, Naguib Mechawar

Childhood abuse and early life adversity are significantly associated with negative mental health outcomes, including depression and suicide. Manifestation of depressive symptoms may be related to altered myelin integrity, as well as changes in glial cell development, activity, and morphology in affected individuals. Since oligodendrocytes are the myelinating cells of the central nervous system, they may play a key role in the changes in myelination associated with child abuse and depression. The uncinate fasciculus is a white matter tract within the limbic system and is the last white matter tract to develop in humans, fully maturing only past the age of 30. Changes in white matter integrity in the uncinate fasciculus have been observed in subjects with depression and related mood disorders, through brain imaging. However, the cellular anatomy and gene expression of the uncinate fasciculus has never been characterized in relation to depression and child abuse. We examined postmortem brain samples with immunohistochemistry, stereology, Western blot, and laser capture microscopy in order to assess differences in expression of myelin-related genes and proteins, as well as oligodendrocyte morphology, distribution, and development between abused and non-abused subjects, compared with healthy controls. Expression of myelin-related proteins, including myelin oligodendrocyte glycoprotein (MOG), myelin proteolipid protein (PLP), and myelin basic protein (MBP), is significantly elevated in subjects that died by suicide and experienced child abuse, compared to subjects that died by suicide but did not experience abuse and healthy controls. These differences may reflect a relationship between child abuse and myelination in the uncinate fasciculus.

A22) Role of Beat Ic in the formation of Drosophila melanogaster hardwired mechanosensory system

Isabela Fabri Karam (*), Junia Vieira dos Santos (*), Brian E. Chen

Introduction: The formation of neuronal circuits relies on two fundamental mechanisms: genetically established functionality and activity-dependent plasticity. Together, these mechanisms orchestrate complex developmental programs that determine single cell identity in a circuit by engaging a wide spectrum of molecular entities (Schreiner et al., 2014). A potential key player is the beaten path Ic molecule, Beat Ic, which was characterized as a positive regulator for axon fasciculation in Drosophila melanogaster motor neurons (Pipes et at., 2001). Nonetheless, its importance in synaptic targeting is not well understood. Thus, our goal is to determine the role of Beat Ic in the formation of Drosophila's hardwired mechanosensory system.

Methods: 455-GAL4 driver was used to selectively express UAS-dsRNA in the scutellum to ensure that RNA interference did not perturb the postsynaptic neural circuitry. Two-day old females were sorted according to their genotype into three groups: 455-GAL4/+ (control group), in 455-GAL4 / UAS-dsRNA Beat Ic (dsRNA Beat Ic), and 455-GAL4 / UAS-TRiP siRNA Beat Ic (TRiP Beat Ic). For the behavioral assay, after decapitation, the flies from dsRNA Beat Ic (n = 35) and the control group (n = 40) were placed in a humidified chamber to recover for one hour, followed by a test for responsiveness of the anterior notopleural (aNp) and posterior scutellar (pSc) neuron's cleaning reflex. The presence or absence of response was scored visually, where a positive response was considered as the successful movement of the rear pair of legs towards the labelled bristles. Additionally, carbocyanine dye labeling was performed in fixed flies of each group (n = 20) to assess the morphology of pSc mechanosensory axons (Kays et al., 2014). Results: In order to assess association between the control and Beat Ic groups, a chi-squared test for independence was performed. Beat Ic had a significantly different cleaning reflex frequency response when compared to control ($p < 0.01$). In terms of morphology, when compared to the control group, Beat Ic experimental groups (dsRNA Beat Ic, and TRiP Beat Ic) consistently presented a strong phenotype, composed of four axonal targeting errors as well as pronounced changes to their axonal harbors, especially primary branches. The phenotype is reliable in terms of morphology and penetrance (70% for dsRNA Beat Ic, and 75% for TRiP Beat Ic).

Conclusion: As demonstrated by our results, Beaten path Ic is involved in the development of the hardwired mechanosensory circuit of the pSc neuron. Further insight might require molecular biology and biochemical experimental assays.

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A23) AB-plaque formation is correlated with grid cell dysfunction and network-level impairment of the medial entorhinal cortex in a mouse model of Alzheimer's disease

Johnson Ying*, Vibha Rao, Kianoush Harandian, Qianzi He, Mark Brandon

Alzheimer's disease (AD) is a debilitating neurodegenerative disease characterized by memory deficiencies, disorientation, and difficulty navigating. One potential circuit-level mechanistic explanation for these symptoms is a disruption of spatial coding in the brain's navigation system that consists of grid cells, head-direction cells, and border cells in the medial entorhinal cortex (MEC). Here, we employed in-vivo electrophysiological recordings in the freely behaving transgenic J20 mouse model of AD which expresses an onset of beta-amyloid (AB) plaques in the MEC at month 4. Most notably, we demonstrate that grid cells are disrupted in aged J20 animals (months 5-6). Furthermore, network-level impairments of non-classified cells in the MEC are present in young J20 animals (months 2-3), preceding the formation of plaques. Our results suggest that the MEC is an important target for future therapies to restore spatial cognitive function in human AD patients.

A24) Brain Networks to Modulate Muscle Co-contraction

Saeed Babadi*, Shahabeddin Vahdat, Theodore Milner

Muscle co-contraction is one of the most salient aspects of neuromuscular control and a key element to modulate the stiffness of the limbs and joints. Co-contraction and how it is regulated during motor learning has been well studied by psychophysical experiments involving adaptation to novel physical environments. However, relatively little is known about the neural substrates of co-contraction. We investigated the neural circuits involved in modulating the muscle co-contraction using a force field motor adaptation paradigm and resting-state fMRI approach. Participants interacted with a robotic interface which created novel dynamics. Kinematics and electromyography were recorded during four different stages of motor adaptation followed by a resting-state fMRI scan that monitored brain activity immediately after each stage was completed. A metric of muscle co-contraction was computed from the normalized electromyographic signals. There was a substantial elevation in co-contraction at the earliest stage of the learning that stiffened the arm and provided stability against unpredictable disturbances. As the learning progressed and the central nervous system gradually became able to generate the appropriate joint torques to counteract the disturbance, the co-contraction level declined. We analyzed the functional connectivity in resting-state networks and demonstrated that change in the strength of functional connectivity in certain brain networks was correlated with a metric of co-contraction.

A25) Maternal symptoms of depression interact with child genetic risk for ADHD in prediction of socio-emotional problems

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Background: Antenatal depression is associated with the offspring's emotional behavioural problems. However, the impact varies across the population, as some children seem resilient. Genetic factors may define vulnerability/resilience to the environment, effects that likely span many molecular pathways. We sought to identify genes and biological pathways that moderate the relationship between prenatal maternal depressive symptoms and emotional behaviours in 60-month-old children.

Methods: This study included 190 mother-child dyads from a cohort with data on maternal depressive symptoms, genome-wide genotyping, and child emotional behaviour. We constructed genetic scores that account for polygenic risk for ADHD and applied them in our gene-environment interaction model. Afterward, we selected a subset of genetic variants that constituted the best-fit genetic score in the interaction model with significance levels less than 0.01 and used MetaCore to examine the enriched gene ontology.

Results: Polygenic risk for ADHD moderated the influence of maternal depressive symptoms on child internalizing problems ($t(186)=3.22$, $p<0.05$). Children with high genetic risk are sensitive to prenatal stress whereas children with low risk are resilient. The most significant genes underlying this moderating effect of the genetic risk score were enriched in pathways and functions related axonal development and synaptic function.

Conclusions: This study suggests that specific genes involved in the biological framework for prenatal neurodevelopment can confer sensitivity or resilience to the influences of maternal antenatal depression.

A26) AβOs Facilitate Neurexin1β Internalization by Interfering Neurexin1β-SorCS1 Interaction

Alfred Kihoon Lee, Yusuke Naito, Raphael Schatz, and Hideto Takahashi

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases. Amyloid-β (Aβ) is a key molecule involved in AD pathogenesis such as synapse loss and synaptic dysfunction. Neurexin (NRX) is a neuronal cell adhesion molecule crucial for presynaptic development and maturation. Our recent study has uncovered that Aβ oligomers (AβOs) directly bind to β-isoforms of NRX1 (NRX1β) at their N-terminal histidine rich domain (HRD), resulting in decreased NRX1β expression on the axon surface and NRX-mediated presynaptic differentiation. Thus, our objective is to define cellular and molecular mechanisms of AβO-induced NRX surface reduction. First, we have uncovered that NRX1β lacking HRD has a lower expression level on axon compared to wild-type NRX1β, suggesting that NRX1β HRD is involved in NRX1β surface expression. To determine whether surface reduction of NRX1β is due to internalization, we next performed an internalization assay using hippocampal neurons expressing HA-tagged NRX1β with AβO treatment. We found that AβOs facilitate NRX1β internalization in axons through interacting with NRX1β HRD. Further, we have uncovered that SorCS1, a regulator of protein trafficking, binds to the HRD of NRX1/2β. Notably, AβOs and SorCS1 competitively binds to NRX1β. Thus, our data suggest that AβOs reduce NRX1β surface expression by competing NRX1β-SorCS1 interaction and consequently facilitating NRX1β internalization.

A27) WHAT IS THE POSSIBLE ROLE OF SILDENAFIL TO REPAIR RETINOPATHY OF PREMATURITY?

Belanger A*, Li S, Poon AWH, Jung S, Balian P, Khoja Z, Polosa A, Lachapelle P, Wintermark P.

Background: Oxygen therapy provided to support the lungs of premature newborns often leads to damages to the retina called retinopathy of prematurity (ROP) and long-term visual impairments. Current treatments for ROP are invasive and aim at preventing further progression of the damages to the retina, but do not repair these damages.

Objective: To investigate the therapeutic effect of sildenafil on retinal structure in a rat model of ROP.

Materials/Methods: Sprague-Dawley rats were exposed to hyperoxia (i.e., 80% oxygen) interrupted by three 0.5-hour periods of normoxia (i.e., 21% oxygen) (hyperoxic animals) per day or room air only (i.e., 21% oxygen) (control animals) from post-natal day 4 (P4) to 14 (P14). Pups were then housed in room air. Sildenafil (50 mg/kg) or vehicle was given per os twice daily after oxygen exposure (from P15 to P21). At P30, retinas were extracted, and sectioned. For retinal histology, eyes were stained with toluidine blue to measure the thicknesses of the different retinal layers. Immunohistochemistry was also performed to count the number of retinal ganglion cells and bipolar cells in the inner retina, as well as the number of astrocytes and microglia within the different layers.

Results: Hyperoxia caused a reduction in thickness of the outer plexiform layer (OPL) and a decrease in the number of bipolar cells in some parts of the retina, compared to control animals ($p < 0.05$); in addition, the number of microglia cells was significantly increased in the rats exposed to hyperoxia, compared to controls ($p < 0.05$). Sildenafil improved OPL thickness in ROP animals, but did not change the number of bipolar cells. In hyperoxic rats treated with sildenafil, the number of microglia were similar to control rats. The number of retinal ganglion cells and astrocytes did not differ significantly between the groups.

Conclusions: Treatment with sildenafil following oxygen exposure provided some recovery of the structure of the retina. This beneficial effect may be modulated by a decrease of inflammation within the retina.

A28) INVESTIGATING THE IMPORTANCE OF CHLORIDE CONDUCTANCE FOR EAAT1 FUNCTION IN VIVO.

Azman Akhter*, Neda Parinejad, Emilie Peco, Tiago Ferreira, and Donald J. van Meyel.

Astrocytes maintain ion and neurotransmitter homeostasis within the central nervous system. They do so by expressing channels, receptors and transporters such as excitatory amino acid transporters (EAATs) along their highly ramified arbors. EAATs are well known to be glutamate transporters, but they have a dual function as chloride channels. The molecular determinants of chloride permeation through EAATs are conserved in the archaeal homologue GltPh, which suggests an important physiological role. However, few studies have addressed the role of chloride permeation through EAATs in vivo, so its importance for normal brain function is not yet completely understood. In a Drosophila model, our lab recently showed that an EAAT1 mutation from a patient with episodic ataxia (EAAT1P>R) caused poor infiltration of neuropil by astrocytic arbors and episodes of larval paralysis (Parinejad, J. Neurosci., 2016). To explore the role of abnormal chloride conductance of the EAAT1P>R mutation in these processes, chloride cotransporters were expressed in astrocytes. Like the EAAT1P>R mutation, the chloride-extruding K-Cl cotransporter KccB also caused astroglial malformation and paralysis, supporting the idea that the EAAT1P>R mutation causes abnormal chloride flow from astrocytes. In contrast, the effects of the EAAT1P>R mutation were rescued by the Na-K-Cl cotransporter Ncc69, which normally allows chloride into cells. These results provide strong evidence that the cytopathology and paralysis in our Drosophila model stem from a gain-of-function chloride channelopathy of glial cells. However, EAAT1P>R affects both chloride conductance and glutamate transport through EAAT1. To specifically investigate the role of the chloride conductance, we are studying a series of mutations that selectively increase or decrease chloride flow through EAAT1 without altering its ability to transport glutamate. We will present our recent findings and ongoing experiments, where rescue and overexpression studies of behavior and astrocyte morphology are being used to test the role of chloride permeation through EAAT1 in vivo.

A29) Pupil dilation to illusory motion in peripheral drift images: Perception versus reality

Steve Beukema*; Jay A. Olson; Ben J. Jennings; Frederick A. A. Kingdom

Peripheral drift is a specific type of illusory motion that causes observers to perceive motion in a static image. We aimed to determine whether pupil dilation occurs during the perception of illusory motion. In three experiments investigating pupil-size changes to peripheral drift, pupil response differences were observed between symmetric patterns (SPs) that elicited no impression of motion and repeated asymmetric patterns (RAPs) that did. All participants reported the perception of motion in the RAP condition and showed significantly greater pupil dilation to these stimuli as compared with viewing stimuli in the SP condition. As a follow-up, we manipulated the RAP stimuli to reduce and then remove the illusion to determine (a) whether it was the asymmetry per se that induced the pupil dilation and (b) whether the amount of pupil dilation was contingent on the amount of observed illusory motion. Although a reduction in perceived illusory motion did not produce a reduction in pupil dilation, removal of the illusory motion did. Despite previous evidence reporting pupil constriction to the perception of motion, and the positive valence associated with symmetry, these experiments show that pupil dilation occurs during the perception of illusory motion. This is in keeping with previous evidence that pupil dilation is influenced by perceptual factors and not simply light level, and, in particular, shows that illusory motion is physiologically arousing.

A30) Long-term modulation of excitability by NMDA receptor signaling in cerebellar stellate cells

Ryan Alexander, John Mitry, Vasu Sareen, Anmar Khadra, and Derek Bowie

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

A31) Collapsin Response Mediator Protein 4 (CRMP4) facilitates neuronal regeneration and Wallerian degeneration following sciatic nerve injury

Marie-Pier Girouard, Mohamad R. Khazaei, Barbara Morquette, Aaron D. Johnston, Nicolas Unsain, Ricardo L. Sanz, Isabel Rambaldi, Marie-Eve Di Raddo, Dianna Willis, Philip A. Barker, Valerie M. K. Verge, Christopher Deppmann, Alyson E. Fournier

In the peripheral nervous system (PNS), damaged neurons can regenerate and reinnervate their target. This process is slow and depends on numerous factors, such as the extent of injury and the distance to the target. Furthermore, efficient recovery requires an appropriate neuronal response to the injury, in which both regeneration and degeneration are initiated and coordinated. It is critical to understand the mechanisms underlying these processes to promote recovery after injury. Thus, we are investigating the roles of Collapsin Response Mediator Protein 4 (CRMP4) in the neuronal response to PNS injury. During development, our lab has shown that CRMP4 promotes axonal growth by interacting with actin and microtubules, and regulating their dynamics (Khazaei et al., 2014, JBC 289(43): 30133). Oppositely, CRMP4 deletion attenuates growth inhibition of dorsal root ganglia neurons induced by chondroitin sulfate proteoglycans (CSPGs) in vitro and promotes regeneration of sensory neurons after spinal cord injury (Nagai et al., 2016, MCN 74:42-8; Nagai et al., 2015, Sci Rep 5:8269). However, the roles of CRMP4 in response to PNS injury are still poorly characterized. We find that different isoforms of CRMP4 are spatially and temporally regulated in the sciatic nerve following injury. In the distal nerve end, calpain-mediated cleavage of CRMP4 occurs early after injury, generating cleavage fragments that may be favoring Wallerian degeneration. Also, in the proximal nerve end, the expression of the long and short CRMP4 isoforms is locally promoted and maintained for up to 14 days after injury, implying a regeneration-associated/growth-promoting role. In support of this, CRMP4 deletion impairs regeneration of the sensory neurons, while also delaying Wallerian degeneration of the myelinated fibers distal to the lesion following sciatic nerve injury. Thus, CRMP4 facilitates the neuronal response to injury by regulating both neuronal regeneration and Wallerian degeneration.

A32) Intersectional genetic labelling of ascending spinal and sensory neuron projections

R. Brian Roome*, Artur Kania

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

A33) An isogenic series of methyltransferase mutations for the study of human neurodevelopmental diseases

Malvin Jefri*; Huashan Peng; Carl Ernst.

Gene expression is explicitly programmed in a specific spatiotemporal patterns and is dynamically modulated throughout neuron differentiation from a progenitor cell state. While much is known about some important genes in neurodevelopment, the integration of how, when, and where gene expression is tuned during human brain development has yet to be elucidated. To address this question, we are deleting eight genes that code forhistone demethylases or histone methyl transferases that are associated with intellectual disability, because genes regulated by these factors are likely critical in normal human brain development. Mutations in histone modifier genes are known to cause robust modifications in global gene expression patterns and may lead to similar transcriptional effects, and similarly dysreulated genes common across two or more histone modifies may point to gene expression levels necessary for normal development. For instance, a mutation in either KMT2D (lysine methyltransferase) or KDM6A (lysine demethylase) causes Kabuki Syndrome - a very particular clustering of clinical features on the autism specturm. This supports the idea that histone modifiers work together to regulate gene expression and some nodes of this network may be common mutations in different genes. We will study this convergence using our previously developed method to rapidly produce induced pluripotent stem cells through simultaneous reprogramming and CRISPR/Cas9 gene editing to create isogenic heterozygous and homozygous knock-out models of histone modifier deficiency disorders and investigate their gene expression patterns using RNAseq at four different developmental stages (iPSC, NPC, and mature neuron). Results from this study may identify a neurodevelopmental program that controls fundamental genes required for neurodevelopment in humans.

A34) Is cortical thickness increased in exceptionally fit older adults?

Kelly Perlman*, Tanja Taivassalo, Russell Hepple, Caroline Paquette

While the aging population shows marked motor and cognitive decline overtime, these changes seem to be attenuated in specific groups of elderly such as in masters athletes (MA) who are physically active older individuals. The aim of this study was to determine whether morphological differences of the cerebral cortex exist between world-class MA over 75 years old, and non-athletic controls (MAC). Fourteen MA subjects (79 SD 5 years old; 8 females) as well as 11 MAC subjects (81 SD 5 years old; 6 females) underwent blood tests to measure circulating factor concentrations and psychological tests including the Mini State Mental Evaluation, Trail Making Test, and Rey Auditory Verbal Learning Test to measure cognitive functioning. All subjects were scanned in a 3T Tim Trio MR scanner (echo time of 2.98 ms; repetition time 2300 ms; flip angle 9 degrees; field of view 256x240 mm; matrix 256x240; voxel size: 1x1x1 mm and 192 contiguous slices, with a 12-channels coil). Morphological differences were assessed via a surface-based cortical thickness (CT) analysis. Each T1-weighted MR scan was processed using the CIVET pipeline (version 2.0.1). SurfStat (http://www.math.mcgill.ca/keith/surfstat/) running on MATLAB was used to conduct mixed linear modelling to model the relationships between cortical thickness and variables such as group, age, serum BDNF concentrations, and cognitive test scores. An ROI analysis was used to contrast frontal regions, using regions segmented with the Desikan-Killiany-Tourville (DKT40) atlas, and compared using two-way repeated measures ANOVAs (group X region). There was no significant difference in whole brain CT between groups, however MA had higher CT in the prefrontal cortex (RFT corrected, $p < 0.01$). Within the MA group only, the cingulate cortex CT is increased with increased serum BDNF concentrations. Mean CT in the frontal regions (superior frontal gyrus, caudal middle frontal gyrus, lateral pars triangularis, lateral pars orbitalis, lateral pars opercularis, lateral and medial orbitofrontal cortex) were significantly thicker in MA as compared to MAC on both the left (MA: 2.735 mm SE 0.030 ; MAC: 2.617 SE 0.034) and the right (MA: 2.762 mm SE 0.032; MAC: 2.642 mm SE 0.036) hemispheres, with multiple comparisons corrected for using Bonferroni. These between-group results point to a protective effect of exercise on the prefrontal cortex, which may be indicative of a slower rate of age-related cortical thinning. Additionally, increased serum BDNF concentrations, which are known to increase as a result of physical activity, seem to play a role in preserving the anatomical integrity of the cingulate cortex in athletes. The specific neural mechanisms that control these effects warrant further investigation, with the goal of optimizing the aging process.

A35) The clinically-available antidepressant mirtazapine alleviates both psychosis and dyskinesia in the MPTP-lesioned marmoset

*Imane Frouni *Stephen Nuara *Nicolas Veyres *Cynthia Kwan *Mery-Jane Harraka *Vaidehi Nafade *Lamia Sid-Otmane *Jim C. Gourdon *Adjia Hamadjida *Philippe Huot

Objective: To investigate the effect of mirtazapine, a clinically-available anti-depressant, on psychosis and dyskinesia in Parkinson's disease (PD).

Background: Psychosis and dyskinesia undermines the quality of life to as many as 50-95% of patients with advanced PD by causing severe morbidity. There is increasing evidence indicating that antagonising serotonin 2A receptors (5-HT2AR) may reduce PD psychosis and dyskinesia. Mirtazapine, a clinically-available anti-depressant, acts through complex interaction with a breadth of pharmacological targets, including 5-HT2AR. Here, we hypothesised that mirtazapine is potentially efficient to attenuate PD psychosis and dyskinesia.

Methods: Parkinsonism was induced to five common marmosets by administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).Stable psychotic-like-behaviours(PLBs) and dyskinesia were induced by daily administration of L-DOPA. Mirtazapine (vehicle, 0.1, 1 and 10 mg/kg) was administered in combination with L-DOPA to the animals, followed by L-DOPA-induced dyskinesia, PLBs and Parkinsonism assessment.

Results: We found that, in combination with L-DOPA, mirtazapine (10 mg/kg) significantly reduced PLBs severity by 50% ($P < 0.01$), when compared to L-DOPA/vehicle treatment. Moreover, mirtazapine (10 mg/kg) significantly reduced duration of on-time with disabling PLBs, when compared to L-DOPA/vehicle (by 64%, $P < 0.001$). Mirtazapine (10 mg/kg) also reduced dyskinesia severity, by 29%, when compared to vehicle ($P < 0.01$). Accordingly, mirtazapine (10 mg/kg) significantly reduced duration of on-time with disabling dyskinesia, by 71%, when compared to vehicle ($P < 0,0001$). Importantly, mirtazapine did not alter the anti-parkinsonian effect of L-DOPA, as measured by parkinsonian disability scores and on-time duration.

Conclusions: These results suggest that mirtazapine is a promising drug candidate to effectively attenuate the severity of PD psychosis and dyskinesia. Since it is already available in the clinic, our results could rapidly lead to proof-of-concept clinical trials in the PD population.

A36) The Effect of Musical Training on Foreign Language Perception and Production

Paul-Noel Rousseau*, Luca Vaquero, Diana Vozian, Virginia Penhune, Denise Klein

Musical and linguistic abilities have been shown to share a similar neural architecture. We were interested if there is a transfer between musical training and linguistic ability and if this is mediated by the age of onset of musical training. Our study was of comprised two musician groups and two groups of English-French bilingual non-musicians classified according to their age of onset of music or language training ("Early- Trained" aoa < 8). Participants completed a rhythm reproduction task, and a Hindi phonemic discrimination and word/sentence reproduction task. Differences in brain structure were assessed with Voxel Based Morphometry (DBM). Behaviourally, we found no group differences on the Hindi discrimination task, but the late-trained musicians did outperform the other groups on the reproduction of Hindi words and sentences. In terms of differences in brain structure, we found structural differences between musicians and non-musicians and within the musician groups in auditory and motor related regions relevant to music and language abilities. Although the results are preliminary, they support previous reports concerning brain differences between musicians and non-musicians and the effects of early musical training. They also contribute the idea of potential transfer effects from musical training to the linguistic domain.

A37) Single-nucleus RNA-seq for measuring altered transcription in the depressed brain

Malosree Maitra(*), Corina Nagy, Gustavo Turecki

Human brain tissue is a heterogeneous mixture of cells with distinct gene expression patterns. Characterization of transcriptional changes caused by psychiatric illness in the brain would benefit from clear differentiation between cell types. Such differentiation is impossible using bulk samples, but single-nucleus RNA-sequencing offers much higher resolution. We are using commercially available droplet-based technology to perform single-nucleus RNA-seq on post mortem brain tissue from depressed patients who died by suicide and healthy subjects. Transcriptomic profiles obtained allow us to identify inhibitory and excitatory neuron sub-types and different classes of glia. Some remaining challenges include ambient RNA amplification and low nuclei capture rates, but optimization of the protocol should allow us to pinpoint transcriptional changes within specific brain cell sub-types in depression and suicide.

A38) Targeted expression of GCaMP6 to map functional retinotopy in the optic tectum of Xenopus tadpoles

Vanessa J. Li*, Anne Schohl, Edward S. Ruthazer

The wiring of the developing Xenopus laevis retinotectal system has been well described anatomically, but the functional organization of the retinotopic map has not been thoroughly characterized. Here we report on the development of an optical approach to visualize retinotopy in the tectal neuropil of albino Xenopus larvae, based on in vivo two-photon imaging of calcium fluorescence changes in response to visual stimulation. By microinjecting messenger RNA for the genetically-encoded calcium indicator GCaMP6 into one blastomer of two-cell stage Xenopus embryos, expression of calcium indicator can be restricted to half of the developing tadpole. Because the projection from the eye to the brain crosses the midline, this approach permits the presynaptic terminals of retinal ganglion cell inputs and the postsynaptic dendritic fields of tectal neurons to be observed independently. Visual stimuli were presented on a LED monitor placed adjacent to the animal under the microscope. Three-dimensional stacks of calcium fluorescence images of the neuropil and tectal cell somata were collected using resonance-scanning 2-photon excitation with piezo focus control, at acquisition rates of up to 30 Hz. The pattern of neuropil fluorescence intensity changes in response to localized visual stimuli were analyzed to extract the spatial map layout in the tectum. The recovered spatial representation in Xenopus tadpoles (stage 48) appear very coarse: different points in the visual field map to largely overlapping tectal area, and the spatial map is compressed at one end of the tectum. The crude mapping may be characteristic of early developmental stages.

A39) The E3 ubiquitin ligase TRAF6 is a novel interacting protein with ALS-linked misfolded SOD1 at the mitochondria.

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Background: Amyotrophic lateral sclerosis is a fatal disease, characterized by the loss of motor neurons and consequent paralysis. Mutations in SOD1 are the second most common genetic cause of ALS. Mutant SOD1 adopts a misfolded conformation and gains toxic properties. Misfolded SOD1 aberrantly associates with and accumulates at spinal cord mitochondria and this correlates with mitochondrial damage. To investigate the underlying mechanisms, we used mass spectrometry to identify novel interacting partners of misfolded SOD1 at the mitochondria in the SOD1-G93A rat model. One candidate, the E3 ubiquitin ligase TRAF6, is already reported to modify mutant proteins in other neurodegenerative disease and has been linked to mitochondrial quality control processes. We hypothesize that the aberrant binding of misfolded SOD1 to TRAF6 contributes not only to mitochondrial accumulation of misfolded SOD1, but that a local loss-of-function of TRAF6 due to misfolded SOD1-mediated sequestration is a potential mechanism underlying mitochondrial toxicity in ALS.

Results: We demonstrate the interaction between misfolded SOD1 and TRAF6 at SOD1-G93A rat spinal cord mitochondria ex vivo. TRAF6-interacting misfolded SOD1 is modified with polyubiquitin and forms high molecular weight species. In vivo co-immunoprecipitation and ubiquitination assays in HEK293 cells show that TRAF6 selectively interacts with and polyubiquitinates SOD1 mutants which exhibit a weakened dimer interface, but not wildtype SOD1 or ALS-linked SOD1 mutants with high dimer stability. Furthermore, co-complexes are partially resistant to detergent and heat, indicating a stable intermolecular bond defines this interaction. Using TRAF6 domain deletion constructs, we elucidated that the TRAF6 C-terminus is necessary and sufficient for the interaction. In silico structural modeling of the TRAF6 C-terminus in interaction with mutant SOD1 predicts that TRAF6 can aberrantly heterodimerize with mutant SOD1 in a manner that is reminiscent of a SOD1 homodimer. We ablated potential binding interface residues in TRAF6 by site-directed mutagenesis and identify Thr-475 as a potential core anchor residue. In vitro interaction assays demonstrate that TRAF6 binds

demetallated but not holo forms of mutant SOD1 directly; the state in which SOD1 is imported into mitochondria. Lastly, we show that TRAF6 is detectable as a 60kDa and a highly abundant 50kDa band in purified rat spinal cord mitochondrial fractions. 50kDa-TRAF6 is particularly abundant in ALS-affected tissues and cell types involved in ALS, resides within mitochondria and co-precipitates with misfolded SOD1 just as 60kDa-TRAF6.

Conclusions: The loss of SOD1 dimer stability has been proposed to be intricately linked to SOD1-related ALS disease severity. Our results suggest that ALS-mutation mediated SOD1 dimer instability is a prequel to the aberrant interaction with and polyubiquitin-tagging by TRAF6. The function of TRAF6 in mitochondrial homeostasis is a new concept and our data indicates that two forms of TRAF6 exist: a full-length form that resides at the cytoplasmic face of mitochondria and a shorter form that localizes within mitochondria. Misfolded SOD1 binds both and we suspect that this will lead to loss of TRAF6 function/s at the mitochondria. We believe that interfering with this binding and restoring molecular dynamics could prove beneficial to motor neuron survival and identify TRAF6 as a new therapeutic target for ALS.

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A40) Excessive lysosomal degradation induced by the Christianson Syndrome mutation NHE6 ΔES impairs AMPA receptor trafficking and structural plasticity in hippocampal neurons

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Proper endosomal trafficking is important for neuronal morphology and plasticity, and deficits in this process have recently been implicated in a number of neurological disorders. This includes Christianson Syndrome (CS), an X-linked neurodevelopmental disorder characterized by intellectual disability, epilepsy, ataxia, and autistic features. Although CS is believed to be one of the most common forms of X-linked intellectual disability worldwide, little is known of its underlying etiology, and intervention for affected individuals is thus lacking. CS is due to mutations in the Slc9a6 gene encoding intracellular sodium/proton exchanger NHE6, which localizes to early and recycling endosomes and regulates their luminal pH. We were the first to show that in hippocampal neurons, NHE6 colocalizes with a subset of AMPA receptors (AMPARs) and is recruited to excitatory synapses following chemical long-term potentiation (LTP). However, the impact of clinical mutations in NHE6 upon neuronal structure and function have not yet been studied. To this end, we are investigating a prevalent NHE6 loss-of-function mutation with deletions of amino acids Glu287 and Ser288 (NHE6 ΔES). Sparse transfection of NHE6 ΔES into primary hippocampal neurons decreased dendritic branching and mature dendritic spine density. Moreover, NHE6 ?ES showed reduced colocalization with early and recycling endosomal markers, yet greater colocalization with markers for late endosomes and lysosomes, which implied an excessive degree of lysosomal degradation. To investigate how this could impact receptor trafficking, we then stained for tropomysin receptor kinase B (TrkB), the high-affinity receptor for brain-derived neurotrophic factor (TrkB). While overall levels of TrkB were comparable, there was a significant attenuation in active phosphorylated TrkB in NHE6 ΔES-transfected cells. This suggested an impairment in BDNF/TrkB signaling, which is crucial for proper spine formation and maturation. Furthermore, NHE6 ΔES expression prevented spine enlargement and AMPAR insertion into synaptic sites following LTP, indicating an impairment in cellular learning mechanisms. However, applying inhibitors of lysosomal degradation to NHE6 ΔES-expressing neurons partially rescued their deficits in dendritic spine density, AMPAR trafficking, and the structural response to LTP. Overall, we find that NHE6 ΔES disrupts the structure and remodeling of hippocampal pyramidal neurons, which may be the cause of learning and memory impairments in CS patients.
Funding: CIHR.

A41) Effect of birth asphyxia on myelination in term newborns

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Background: Birth asphyxia refers to the insufficient delivery of oxygen and/or blood to different body organs, including the brain, around the time of birth. Birth asphyxia can lead to death and brain injury, leading to long-term neurodevelopmental problems such as cerebral palsy and cognitive impairments. Currently, the impact of such brain injury on brain myelination is unknown.

Objective: To assess myelination over the first month of life in term asphyxiated newborns treated with hypothermia.

Methods: We conducted a prospective cohort study of term asphyxiated newborns admitted to the neonatal intensive care unit between 2014 to 2017 and treated with hypothermia. When possible, brain magnetic resonance imaging (MRI) was performed for these newborns around day of life (DOL) 2, 10, and 30. Myelination was measured using T2*-weighted imaging in various regions of interest in the cerebrum: i.e., posterior limb of the internal capsule (PLIC), genu and splenium of the corpus callosum, thalamus, lentiform nucleus, and anterior and posterior white matter (WM). Myelination levels were then compared between asphyxiated newborns with brain injury (BI) and asphyxiated newborns without brain injury (NBI).

Results: Comparison according to time-point of the MRI: Among asphyxiated newborns with brain injury, myelination was significantly decreased in the PLIC on DOL 10 ($p = 0.023$) and DOL30 ($p = 0.033$). There was also significantly less myelination in the genu and splenium of the corpus callosum on DOL10 (both $p = 0.0085$) compared to those without brain injury. No significant differences in myelination between the two groups were found in the thalamus, lentiform nucleus, and anterior and posterior WM across all time-points. Comparison according to corrected gestational age (CGA) at the time of the MRI: Myelination significantly improved over time in the thalamus in both NBI ($r = -0.45$, $p = 0.012$) and BI groups ($r = -0.57$, $p = 0.0006$); there was no significant difference in myelination between the two groups in this ROI. Myelination significantly improved over time in the PLIC and lentiform nucleus for the BI group ($r = -0.53$, $p = 0.0018$; $r = -0.47$, $p = 0.0061$, respectively); however, there was no significant change in myelination over time in the NBI group. No significant correlations were found between the NBI and BI groups at the level of the genu and splenium of the corpus callosum, nor both the anterior and posterior WM.

Conclusion: Birth asphyxia and subsequent brain injury disturbed myelination in term asphyxiated newborns treated with hypothermia, suggesting that birth asphyxia, in addition to causing direct brain injury, also impaired normal brain development. Future research should investigate if these changes are temporary or persistent.

A42) Brain tumor location affects resting-state functional connectivity

Daniel Di Giovanni*, Louis Collins, Denise Klein

The gold standard for preoperative planning in brain surgery is to map functional cortex with direct intraoperative electric stimulation. Unfortunately, this involves an invasive procedure. Recently to overcome this, task-based functional magnetic resonance imaging (fMRI) has been used preoperatively to delineate eloquent cortex. Although non-invasive, this also has several short comings as it is both labor and time intensive to find and use appropriate tasks, as well it is limited to patients that can preform these tasks. Resting-state fMRI (rs-fMRI) has been proposed as a surgical planning method to overcome these limitations. Such a method can improve surgical planning while remaining non-invasive. Studies show that network connectivity is altered in the presence of tumors, but little work has been done to quantify the exact effect of tumor location on these alterations. This project examines the effect of tumor location on the anti-correlation between the default-mode network (DMN) and task-positive areas. We collected rs-fMRI data from 42 tumor patients and compared them to 23 healthy controls, using both seed-based analysis and ICA analysis of network connectivity. The data demonstrates that tumors in areas associated with the DMN disrupted the anti-correlation to task-positive areas, which suggests that tumor location has a widespread effect on functional connectivity.

A43) ProBDNF and mBDNF signaling underlie distinct activity-dependent processes in visual circuit development

Elena Kutsarova*, Martin Munz , Anne Schohl, Alex Wang, Yuan Yuan Zhang, Olesia Bilash, Carmelia Lee, Edward Ruthazer

Sensory experience instructively refines topographic representations of the sensory world in the brain. Correlation in the firing of presynaptic inputs leads to the stabilization of synaptic contacts. Asynchronous firing of presynaptic inputs can lead to synaptic weakening and facilitates exploratory axon branching and growth, favoring the pruning and retargeting of inappropriate connections. Brain-derived neurotrophic factor (BDNF) is synthesized as precursor protein (proBDNF) and consequently cleaved to its mature form (mBDNF). Tissue plasminogen activator (tPA) and plasmin are believed to participate in the extracellular conversion of proBDNF to mBDNF. BDNF is a well-known modulator of synaptic efficacy with mBDNF signaling through TrkB to enhance synaptic strength and proBDNF working through p75NTR receptor to promote synaptic weakening. We used in vivo multiphoton imaging of retinal ganglion cell axonal growth in Xenopus laevis tadpoles, in conjunction with various visual stimulation paradigms to reveal the molecular mechanisms underlying synchrony-induced (Hebbian) stabilization and asynchrony-induced weakening of retinotectal inputs. TrkB-Fc injection to sequester endogenous BDNF prevents Hebbian stabilization of axonal branches. Presynaptic knock-down of p75NTR impairs both axon branch additions and eliminations, leading to an increase in branch density over 4 days. Our preliminary data suggest that proBDNF and mBDNF signaling may have opposing functions in asynchrony and synchrony-induced structural remodeling to encode proper circuit refinement.

A44) ASSESSMENT OF SPINAL HOMER PROTEINS AND mGLUR5 IN NOCICEPTION

Nitasha Gill BSc*, Andre Laferrière BSc, Virginia M. Cornea PhD, Terence J. Coderre PhD

In neuropathic and inflamed animals, there was a significant increase in nuclear mGluR5 expression. This increase can be explained by the actions of proteins that affect mGluR5 trafficking. Homer proteins regulate trafficking and intracellular signaling associated with mGluR5. Induction of Homer1a has been shown to affect localization of mGluR5. Acutely, Homer1a acts homeostatically to prevent glutamate-induced excitotoxicity. Homer1a induction causes synaptic remodeling which may actually lead to the development of nociceptive hypersensitivity after nerve injury. This provides the rationale for our investigation into the modulatory role of Homer1 proteins on cell surface and nuclear mGluR5 in nociception. We hypothesize that Homer1a and Homber1b/c affect the signaling and trafficking of cell surface and nuclear mGluR5 which leads to the development of nociceptive hypersensitivity after nerve injury. To determine whether Homer1a plays a role in the nociceptive mechanisms in the spared nerve injury (SNI) model, lumbar tissue was extracted from SNI rats 4 h and 24 h after nerve injury. Homer1a protein was found to be significantly elevated in SNI rats 4 h after the injury but not 24 h afterwards. To assess whether a Homer1a mimic peptide, TAT-mGluR5ct, is able to reduce nociceptive hypersensitivity, TAT-mGluR5ct was injected intrathecally (L4-L5) at various dosages (0 ng, 3 ng, 30 ng, 3 ug) in naive rats. 30 minutes later, 20 nmol of quisqualate was injected intrathecally (L4-L5). Sustained nociceptive behaviours were recorded for a period of 30 minutes. TAT-mGluR5ct dose-dependently reduced quisqualate-induced sustained nociceptive behaviours. Taken together, Homer1 appears to play an important role in mGluR5-related nociceptive hypersensitivity and warrants further study.

A45) Placental Group B Streptococcus Infection: Sex Specific Inflammatory Response and Autistic-Like Traits in Male Offspring

Marie-Julie Allard*, Antoine Giraud, Clemence Guiraut, Mariela Segura, Guillaume SÃ©bire

INTRODUCTION: Group B Streptococcus (GBS) infection is one of the major causes of chorioamnionitis, which is a risk factor for preterm birth and autism spectrum disorder (ASD). Chorioamnionitis affects the placental synthesis of neurotrophic factors, and triggers the release of neurotoxic inflammatory mediators, such as interleukin-1 (IL-1), which might disrupt myelinated neuroglial fiber tracts. We previously showed, using a new rat model, that GBS-induced maternal infection leads to sex-specific forebrain injuries and ASD-like traits in the offspring (Allard et al., Autism Research, 2016). Our hypothesis is that maternal exposure to GBS impacts the placenta through an IL-1 driven inflammatory response leading to brain injuries and ASD in the offspring. OBJECTIVE: To characterize GBS-induced inflammation on the placenta, and its effect on the offspring brain.

METHODS: Dams were inoculated intraperitoneally on gestational day (G) 19 with serotype 1a GBS (108 CFU). Caesarian-sections were performed at G20, G21 and G22 to collect placental, maternal and fetal blood samples. The maternofetal infectious/inflammatory responses were characterized by Gram staining, immunohistochemistry and ELISA. Offspring born naturally performed ASD-oriented behavioral tests, and their brains were collected at postnatal day (P) 40 for histological studies.

RESULTS: Placentas of GBS-exposed dams were infected, but did not result in pups? infection. GBS-exposed dams displayed chorioamnionitis characterized by a higher infiltration of polymorphonuclear cells in male than female placentas. Following GBS infection, increased titers of IL-1? were detected in maternal blood, male placentas, and male fetuses? blood, vs control tissues. Forebrain injuries were observed in the male offspring exposed to GBS compared to controls: enlarged lateral ventricles adjacent to thinner external capsules and corpus callosum, and increased thickness of cingulum and larger area of the left hippocampus.

CONCLUSION: Exposure to live GBS induces maternofetal immune activation resulting in neurodevelopmental abnormalities recapitulating those of human ASD, including sex dichotomy and behavioral phenotype. Our findings pave the way towards the use of IL-1 blockade in therapeutic trials aimed to prevent ASD arising from GBS infection, a common and modifiable gestational environmental factor.

A46) Astrocyte MiRNA Profiling in Multiple Sclerosis and Normal Human Brains

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Astrocytes play a major role in the development of the Multiple Sclerosis (MS) lesions by secreting molecules that regulate immune and pro- and anti-inflammatory responses, by protecting cells and tissues from damage, by contributing to repair, and by forming glial scars when tissues are destroyed. MicroRNAs (miRNAs) are small, non-coding RNAs that regulate gene expression post-transcriptionally. We have previously demonstrated differential astrocytic miRNAs profiles in different regions and developmental time points of normal human brains using a selected panel of miRNAs. The selected miRNAs included those which are mediators of inflammation and some that are upregulated in ischemia and may serve a neuroprotective role. MiRNA profiles of white matter astrocytes captured from active, chronic active, and inactive lesions were compared with those from normal controls. The analysis of in-situ miRNA expression in astrocytes shows distinct pathology oriented patterns of expression. In contrast to microglia, the inflammation mediating miRNAs, miR-155 and miR-146a were lower in MS cases compared to controls. Ischemia-related miRNAs, miR-34a, miR-210, and miR-214 were upregulated only in active MS lesions compared to controls. Astrocytes are considered to protect neurons and glia from the tissue hypoxia/ischemia which probably plays a role in MS pathogenesis. MiR-210 has been shown to upregulate growth factors (e.g. VEGF, known to be upregulated in MS) production by astrocytes. We believe our data suggest a neuroprotective role for astrocytes during the acute phase of lesion development in MS.

A47) Functional behaviour of brain-specific Nav1.5 voltage-gated sodium channels

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While the voltage-gated sodium channel Nav1.5 is recognized mainly for its contribution to the cardiac action potential, it is also expressed in the brain, where its role remains largely unexplored. Nav1.5 is subject to alternative splicing at exon 6, such that Nav1.5 retains exon 6b while the splice-form Nav1.5e acquires exon 6a instead. This alternative splicing may have repercussions on neuronal firing, given that the main difference is a ~10 mV depolarizing shift in the activation profile of Nav1.5e relative to Nav1.5. The two splice-variants differ at 7 amino acid residues, all of which are located in the voltage sensor of domain I. Even though these residue exchanges occur in a part of the channel which is critical for pore opening, their specific structure-function relationships are not fully explored. We engineered single point mutations, introducing key amino acids from Nav1.5e into Nav1.5, and identified that an aspartate-lysine switch contributes the most to the altered gating profile. This study illustrates the mechanism by which alternative splicing in domain I modulates the functional properties of Nav1.5, which may in turn contribute to the fine-tuning of cell excitability.

A48) Investigation of sex differences in the contribution of spinal atypical PKCs to persistent nociceptive sensitization

Nicole George*, Terence Coderre

Introduction: Chronic pain is an overwhelmingly prevalent health concern, as well as an economic burden, largely due to the fact that the underlying pathophysiology remains unclear. One strategy to determine new targets for analgesic relief has been to examine the maintenance of pain hypersensitivity. Pain chronicity and long-term memory share similarities in the mechanistic underpinnings of synaptic plasticity. Protein kinase M zeta (PKM zeta), a persistently active atypical PKC, has been implicated in both the maintenance of hippocampal LTP and memory, in addition to maintaining the spinal nociceptive sensitization that underlies pain hypersensitivity. However, hippocampal studies have established a compensatory mechanism by PKC iota, another atypical PKC. To date, no studies have investigated the role of PKC iota in spinal nociception. Moreover, PKM zeta-dependent sex differences propose that females may rely on mechanisms other than PKM zeta for the maintenance of spinal nociceptive sensitization. Thus, the purpose of this study is to examine the contribution of spinal PKC iota in both male and female rats, using behavioural assays in models of inflammatory pain and referred muscle pain.

Methods: Male and female Long Evans hooded rats were used for all procedures. Formalin testing was used to assess inflammatory pain. Naïve rats received an intrathecal injection (20 μL) of either PKC iota specific inhibitor ICAP (20 nmoles/20 μL) or sterile water 25 minutes prior to the intraplantar injection of 50 μL of 2% formalin. Sustained nociceptive behaviours (SNBs) were assessed using the weighted means scoring method every 3 minutes for a total of 46 minutes. Referred muscle pain was assessed through intramuscular (i.m.) acidic saline (0.9% NaCl in sterile water, pH adjusted to 4.0). Two i.m. acidic saline injections (100 μL) were administered to the gastrocnemius muscle, separated by five days, to induce persistent hind paw mechanical allodynia. Intrathecal injection of ICAP or sterile water was given 24 hours after the second acidic saline injection. The level of mechanical hypersensitivity was measured by investigating paw withdrawal threshold, using an up-down procedure with von Frey hairs, for a period of 4 weeks.

Results: Significant reductions in SNBs were found in males for the formalin test, while no effect was shown for females. Testing of referred allodynia is ongoing, but is expected to be similar to the formalin test.

Conclusion: This research aims to determine how the pharmacological inhibition of spinal PKC iota influences centrally-mediated persistent pain induced by inflammatory agents or referred muscle injury, across males and females. Given the clinical relevance of chronic pain conditions in females, investigation into sex-specific mechanisms is necessary step in drug development for analgesic relief.

A49) Modification of the adult rat tonotopic map through passive sound exposure impairs performance on a tone discrimination task

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After maturation, the rat auditory cortex exhibits a stereotypical tonotopic map that remains stable throughout life. However, housing adult rats in broadband white noise has been found to have a profound plasticity-inducing effect on this map. The current study used a behavioral paradigm to test the hypothesis that passive noise exposure can be used as a tool to improve learning in adult rats. First, we showed that a two-week exposure to noise followed by a one-week exposure to 7kHz tone pips was sufficient to produce an overrepresentation of the 7kHz frequency region in the tonotopic map of a group of adult rats. Next, we trained one group of exposed and one group of non-exposed rats on an adaptive tone discrimination task where the target tone was 7kHz. In previous paradigms with this design, learning was associated with an overrepresentation of the target tone in the tonotopic maps of trained rats. Thus, our expectation was that exposed rats would have an advantage on this task because of the induced early overrepresentation of the target tone. Contrary to our expectations, however, we found that exposed rats had poorer behavioral performance. Despite responding to the target tone at the same rate as non-exposed rats, they were not able to suppress their response to non-target tones. This performance was accompanied by electrophysiological changes in auditory responses that also demonstrated reduced discriminability of the overrepresented tone. These results suggest that passive exposure to noise can lead to maladaptive plastic changes in the auditory cortex that can affect performance and behavior.

A50) The Effect of Chronic Altered Diurnal Light on Motor Coordination and Cognitive Functions in Aged Mice

Tara Delorme, Geneviève Dubeau Laramée & Nicolas Cermakian

Brain ageing leads to the degradation of many brain systems, including the suprachiasmatic nucleus, which is the mammalian master circadian clock that governs daily cycles in physiology, brain function and behaviour. We investigated the link between circadian disruption and neurological ageing by exposing mice to different chronic altered diurnal light cycles and measuring their performance on tests of motor and cognitive function. Mice were raised since youth in one of three conditions: a) an optimal diurnal environment of 12 hours of light and 12 hours of dark; b) a "light-polluted" environment, where the dark period was contaminated by dim light; and c) a "social jetlag" environment with weekly cycles of 5 days of 9 hours of light and 15 hours of dark, followed by 2 days of 15 hours of light and 9 hours of dark. After one year in these environments, we conducted seven behavioural tests on all mice and compared all aged groups to one another and to a cohort of young mice. Differences were found between young and old mice in the grip strength ratio (p<.01), but not in the balance beam test for both the 0.5-inch beam (p=.87) and the 0.25 inch beam (p=.13) or in the elevated plus maze (p=.056). The "light polluted" group and the young mice showed lower locomotion in vertical activity **(**p<.01). Finally, in the Morris Water Maze, a main effect of quadrant (p<.01) was found but there was no significant interaction between group and quadrant (p=.054). Results for prepulse inhibition of acoustic startle and novel object recognition are being analyzed and will be presented. Our work indicates alterations in aged mice after chronic circadian disruption.

A51) Prior sub-threshold psychotic symptoms associated with thicker right, inferior frontal gyrus among patients in a first episode of psychosis

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Background: Individuals with attenuated positive and sub-threshold psychotic symptoms (APSPS) are considered at-risk for psychosis. However, few studies of first episode psychosis (FEP) differentiate between FEP patients with and without a reported history of APSPS (APSPS+ and APSPS-, respectively) before onset. Recently, we found that compared to APSPS- patients, APSPS+ patients had worse functional outcome after two years of treatment despite comparable symptom relief. Because our results provides evidence for APSPS history as a clinically meaningful factor in FEP outcome, we wanted to explore whether prior APSPS offered any neurobiological insights. While imaging studies on at-risk youth and FEP patients reveal progressive trends in cortical thinning across stages of illness, none have considered the APSPS history of FEP patients. To better understand neurobiological trends across illness stages, we investigate the implications of APSPS+/- history in the cortical thickness of FEP patients using a whole-brain approach.

Methods: Patients (N=73) were recruited from PEPP-Montreal, a FEP clinic at the Douglas Mental Health University Institute. The Circumstances of Onset and Relapse Schedule was administered to identify youth who recalled at least one of nine expert-selected APSPS prior to their FEP (APSPS+). Patients were scanned at baseline evaluation and structural T1-weighted images were processed through the CIVET 2.1 pipeline. Tlaplace thickness values were employed for group analysis. Whole brain, vertex-wise unpaired t-tests were performed between groups (N=51 APSPS+, 22 APSPS-), controlling for age, sex, and mean whole-brain thickness. Significant clusters were identified with a threshold of 0.01.

Results: Analyses revealed that APSPS+ patients had a significantly thicker right, inferior frontal gyrus (sub-region of the prefrontal cortex) compared to APSPS- patients (p=0.01). No other significant group differences were found elsewhere.

Conclusions: Thicker right, prefrontal cortex among APSPS+ patients may indicate abnormal cortical maturation that may give rise to, or suggest vulnerability to, sub-threshold psychotic symptoms. In addition to suggesting differential underlying neurobiology related to APSPS, these results suggest the importance of considering APSPS history, in addition to FEP symptomology, in mapping the trajectories of changing cortical thickness among FEP patients.

Funding: CIHR, IPN

A52) Role of inhibition in the songbird motor pathway

Gaurav Isola

Many complex motor behaviours like singing or speech have a hierarchical organization, of which HVC (proper noun), a higher order nucleus plays a key role in the singing of songbirds. Inhibition within HVC is known to be important for song motif sequence generation but the underlying mechanisms are poorly understood. It is also known that it precisely controls the temporal aspects of the song, however, the extent to which it controls the structural aspects of the song is not studied extensively. Here we are manipulating the levels of inhibition within HVC by infusing Muscimol ($GABA_A$ agonist) by using reverse microdialysis technique. We see that Muscimol concentration affects the amount of singing since birds stop singing at high doses. Whereas at lower doses, the amount of singing reduces but the bouts of song produced are comparable to the song without Muscimol. Nevertheless, at certain concentrations, we observed that the birds continue to sing, but a degraded version of the song. To explain the visualized degradation of song structure, we quantified the effect of Muscimol on these features across all the song syllables: mean Duration, mean Entropy, mean Amplitude, mean Amplitude Modulation, mean Pitch and mean Pitch Modulation. The results indicate that manipulating levels of inhibition in HVC does affect the temporal as well as structural features of the song

A53) Sensitive Periods of Language Acquisition: Effects on foreign language learning

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There is evidence that there is a sensitive period for second language acquisition: an optimal age range when learning confers long-term benefits in fluency. The aim of the present investigation is to explore important differences in the bilingual experience based on age of second language acquisition, which fundamentally shapes the way language is represented in the brain and the abilities of the speaker. The question asked here is whether there is a "simultaneous bilingual advantage" when learning a new foreign language due to the acquisition of a second language earlier within the sensitive period. Two groups of bilinguals were compared; 10 simultaneous bilinguals, who learned both English and French from birth, and 11 sequential bilinguals, who learned French from birth and English after the age of 7. All have native proficiency in both English and French and no experience in a third language or exposure to the experimental languages. Participants were tested on a Hindi phoneme discrimination task in which they had to distinguish a dental-retroflex contrast that is phonemically distinct in Hindi, but perceptually very similar for non-native speakers. Following a familiarization period, they were asked to discriminate the two sounds. Participants also completed a word and sentence repetition paradigm in which Hindi words or sentences were presented three times, and the participant was required to produce the word or sentence to the best of their ability. Three native speakers of Hindi subsequently rated the speech produced by the participants. All participants also completed a resting state functional connectivity scan to investigate intrinsic networks within their brains. The simultaneous bilinguals outperformed their late-trained counterparts on the phoneme discrimination task, but both groups performed similarly on word and sentence repetition tasks. This study sheds light on the behavioral and neural differences between these two types of bilinguals, and shows how differences in experience, such as the age at which a language is learned, shape our brain organization. In the larger context, this study aims to aid education, to encourage learning during the sensitive periods for optimum cognitive benefits, and advocate for children to begin learning complex skills at a young age.

A54) What we say matters: Stakeholder perspectives on media coverage and public understanding of fetal alcohol spectrum disorder

J. Aspler[12], A. Bogossian[1], and E. Racine[123]:

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Objectives: Aim 1: To explore the lived experiences, beliefs, and perspectives of Canadians with fetal alcohol spectrum disorder (FASD) and other key FASD stakeholders. Aim 2: To understand the views of key FASD stakeholders regarding Canadian media coverage of both FASD and alcohol consumption during pregnancy.

Background: FASD, a complex diagnosis that covers a wide range of neurodevelopmental disabilities, results from a fetus' exposure to alcohol in the womb. Although existing evidence suggests that FASD affects roughly 1 in 100 Canadians, more recent studies indicate that the number could be higher.

While Canadians know that FASD exists, and that drinking alcohol when pregnant can harm a fetus, they are less informed about what FASD actually entails. Given this gap in knowledge, the media, a common source of information thought to impact and reflect public attitudes, could play a key role in shaping the way the public understands FASD. In addition, given the media's history of poorly portraying people with disabilities, it could be one factor in the generation of stigma toward vulnerable groups such as people with FASD and women who drink while pregnant. In the latter case, stigma could result in connection with the fact that prenatal alcohol exposure is a necessary factor in the development of an FASD.

Methods and preliminary results: We conducted twelve, two-hour-long semi-structured focus group interviews equally divided among three key stakeholder groups: 1) adults with FASD; 2) adoptive and foster parents of people with FASD; and 3) healthcare professionals with experience caring for people affected by FASD. The interviews focused on: 1) stigma and labelling (e.g., how people with FASD feel the label impacts them, how physicians feel about providing diagnoses); and 2) reflections on specific media quotes we provided during the interviews. This poster will report results in these areas based on a preliminary data analysis.

Session B: Thursday 7:00-8:00pm, Friday 1:25-3:15pm

B1) Glial HO-1: A driver of Parkinson-like neurodegeneration in aging mice

Marisa Cressatti, Wei Song, Adrienne Liberman, Carmela Galindez, and Hyman M. Schipper

Idiopathic Parkinson disease (PD) is a movement disorder that afflicts 1-2% of the population over 65 years of age. Epigenetic effects mediating brain iron deposition, oxidative mitochondrial injury and macroautophagy in PD and related conditions remain enigmatic. Here we show that selective overexpression of the stress protein, heme oxygenase-1 (HO-1) in astrocytes of GFAP.HMOX1 transgenic mice between 8.5 and 19 months of age results in a parkinsonian phenotype characterized by basal ganglia siderosis; oxidative stress; mitochondrial damage/mitophagy; nigrostriatal hypodopaminergia associated with locomotor incoordination and stereotypy; downregulation of TH, DAT, LMX1B, Nurr1 and Pitx3 mRNA and/or protein; and overproduction of alpha-synuclein mRNA and protein. We also identified altered levels of key brain microRNAs which may be responsible for the aberrant expression of Nurr1, Pitx3, DAT and alpha-synuclein in these mice. Many of the molecular changes we observed in the intact GFAP.HMOX1 brain were recapitulated in isolated neurons co-cultured with *HMOX1*-expressing astroglia indicating further that patterns of neuronal dysfunction commensurate with parkinsonism may be evoked by a primary insult to the astroglial compartment. Our findings raise the possibility that curtailment of glial HO-1 transduction may confer neuroprotection in idiopathic PD and other chronic CNS disorders."

B2) The EEGapp Software: An EEG Analysis and Processing Pipeline

Yacine Mahdid* and Dr. Blain Moraes

Accurate analysis of electroencephalographic (EEG) data requires detailed training and domain expertise. This high knowledge requirement prevents some researchers from using EEG techniques in their research and lead those that do not have proper training to erroneous results. Although program have been built to facilitate basic EEG analysis for non-experts (e.g. Brainstorm, eeglab, Chronux), recent advances in analysis techniques are not included in these software packages. The goal of this project is to build a computer program that can automatizes the analysis of EEG data in order to reduce the workload of experts and the possible errors that arise while self-coding the analysis techniques. To build the EEG analysis and processing pipeline (EEGapp) we made use of the open source software eeglab to structure EEG data and the Matlab programming language to implement various analysis techniques: spectrogram, topographic map, functional connectivity (i.e. PLI), directed functional connectivity (i.e. dPLI), coherence, symbolic transfer entropy (STE), phase amplitude coupling (PAC) and graph theory analysis. These were tested rigorously with previously analyzed EEG data and the software was sent to other researchers for independent testing. We reached out to the target audience through conferences and distribution of EEGapp on the BIAPT's lab website. From the feedback we received, we conclude that the reception is positive and that this software would be useful to researchers in the field.

B3) Hippocampal volumes in youth with congenital heart disease

Fontes, K [1-2]. Kesraoui, L[2]. Chakravarty, M[1, 5-7]. Brossard-Racine, M[1-4].

BACKGROUND: Congenital heart defects [CHD] are the most common prenatal malformations and a leading cause of neurodevelopmental impairments. While adolescents and adults with CHD often present with executive function deficits and have an increased risk for psychiatric disorders, there are only a limited number of studies which have evaluated brain structure integrity in this population. With the hippocampus playing a crucial role in learning and memory, we sought to compare hippocampal volume using quantitative magnetic resonance imaging [MRI] between emerging adults born with a CHD and age- and sex- matched healthy peers. We hypothesized that youth born with CHD would have smaller hippocampal volumes than controls.

METHODS: Adolescents born with CHD (n=32) at a mean age of 19.7y and healthy matched controls (n=23) at a mean age of 20.1y underwent brain MRI at the Montreal Children's Hospital of the McGill University Health Centre [MCH-MUHC]. Images were quantitatively analyzed using a Multiple Automatically Generated Templates brain segmentation algorithm [MAGeT-Brain] for total brain and hippocampal volumes. Associations between volumes and clinical variables were assessed in the CHD group. RESULTS: We observed widespread significant reduction in total brain volumes and in total hippocampal volumes in the CHD group when compared to healthy controls. The hippocampal subfields segmentation showed a significant volume reduction in both the left and right Cornu Ammonis 4 [CA4] and the dentate gyrus, as well as, the left stratum. Cyanosis at birth and total number of catheterizations, correlated significantly with total hippocampal volumes. However, other clinical variables, such as, age at first open heart surgery and presence of deep hypothermic circulatory arrest did not correlate with hippocampal volumes. There was also a strong positive correlation between brain anomalies detected on conventional MRI and hippocampal volume.

CONCLUSIONS: Adolescents born with a congenital heart defect having undergone cardiopulmonary bypass surgery before 2 years of age show a significant decrease in total brain volume and in specific brain regions such as the hippocampus, suggestive of long-term alterations in brain structure. Further research should seek to explore structure function relationships between the hippocampus and functional outcome to address the daily limitations faced by adolescents with CHD.

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B4) Epidemic Spread Models Predict the Atrophy Pattern in Parkinson's Disease

Ying-Qiu Zheng*, Yashar Zeighami, Yu Zhang, Bratislav Misic, Alain Dagher

Introduction Parkinson's Disease, the second most common neurodegenerative diseases, is widely accepted as a result of the progressive accumulation of alpha-synuclein aggregates. A number of studies have shown that the toxic aggregates can spread from region to region through human connectomes and infect normal alpha-nuclein, leading to dysfunction and finally neuronal death of the regions where the protein deposits are present. However, the exact mechanisms underlying the pathogenic spread of alpha-synuclein, and the relationship between alpha-synuclein deposits, neuronal vulnerability, and atrophy pattern are yet to be found. In our study, we have developed several parameterless epidemic models on human connectomes to simulate the pathogenic spread of the alpha-synuclein aggregates. We found that the models, when integrated with relevant gene expressions levels, nicely replicate the atrophy patterns in PD patients. This partly corroborates the well-accepted hypothesis of the pathogenic spread of toxic alpha-synuclein as the cause for the neuronal loss in Parkinson's Disease. Methods Brain Network Regions The brain regions in which toxic alpha-synuclein aggregates infect the normal ones are adapted from a multimodal parcellation developed by Cammoun et al., 2011[1]. We excluded the right hemisphere to improve the accuracy of white matter estimation and gene expression parcellation, resulting in a total of 42 regions of left hemisphere as the basis framework of our epidemic models. Edges The human connectome, which reflects white matter estimation, is constructed by running deterministic tractography on a template of 842 individual diffusion Magnetic Resonance Imaging (dMRI) data from Human Connectome Project (HCP) in DSI-Studio[2]. The template is reconstructed by averaging the spin distribution function of individual dMRI data estimated by using generalized q-sampling imaging (GQI). The tractography is seeded from each region respectively with a fixed step of 0.5mm, and terminated if the quantitive anisotrophy exceeds 0.05 or the turning angle is sharper than 55/0.5mm. This ended up with two connection matrices: one contains tracts length between each pair of regions, and the other contains tracts density normalized by the area of the regions they connect. Gene expression levels SNCA, a gene that controls the synthesis of normal alpha-synuclein, and GBA, a gene that codes for lysosome which clears normal and aggregates of alpha-synuclein, are incorporated in our spread model to control the synthesis rate and clearance rate of the proteins in each region. The gene expression maps, provided by Allen Brain Institute, are obtained by averaging the gene expression z-scores of six postmortem brains (left hemisphere only) in each ROI of our template. SIR Epidemic Model We developed a Susceptible-Infected-Removed(SIR) model to simulate the epidemic spread. The process includes the three following modules: 1)the growth of normal α-syn in each region. Considering normal brains have certain levels of α-syn concentration in each area, we solve the following equations to determine the density level of normal α-syn in each ROI as the initial condition for disease propagation:[equation] 2)The spread of misfolded α-syn aggregates and the infection of normal α-syn, which are described as:[equation] 3)The neuronal loss caused by the accumulation of the toxic aggregates of misfolded α-syn. Here we took the ratio $M_{i}/(N_{i} + M_{i})$ as the overload of misfolded α-syn in region i and $1 - \exp(-M_{i}/(N_{i} + M_{i}))$ as the neuronal loss in unit time. The total

neuronal loss at time T in each region could be expressed as:[equation] Notably, the absolute values of the measures above have no real meaning. We only care about the relative concentration of misfolded α-syn and neuronal loss in each region to compare with the real atrophy pattern in PD patients. Agent-based SIR Model We also developed a random walk SIR model to simulate the epidemic spread. Each protein, either normal or misfolded, is modeled as an independent agent that could diffuse between regions and contact each other. At each time step, agents transit to other states according to the following probabilities:[equation].The length of white matter tracts between region i and j determines the duration agents stays inside the path before entering the regions. In the meanwhile, new agents are generated with probability $\alpha_{i}\delta t$ in region i. Results The numerical solutions of the SIR model replicate the real atrophy pattern in PD patients. We solve equation (1) to derive the concentration of normal ?-syn in each region as the initial state for the SIR model. For equation (2)(3), a simple analysis reveals that the system will converge to a stable point. Setting the initial number of misfolded protein to 1 in seed region, we solve (2)(3) to find the stable state of the overload of misfolded alpha-syn. The numerical solutions of neuronal loss nicely replicate the atrophy pattern in PD patients. [pictures and illustrations] Permutation test reveals GBA and SNCA as relevant factors to account for the pathogenic spread. To test the significance of GBA's effect on the clearance of alpha-syn, and SNCA?s effect on the synthesis of normal alpha-syn, we run permutation test for both of the genes separately. We relabeled the gene expression scores across the regions and plotted the distribution of spearman correlation coefficients between the real atrophy pattern and the simulated neuronal loss based on the randomized gene expression maps, leading to the conclusion that the ?ground truth? of GBA and SNCA maps do produce significantly higher correspondence than the randomized gene expression maps. [pictures and illustrations] The random walk SIR model shows Substantia Nigra as the most likely epicenter of the pathogenic spread in Parkinson's Disease. To make the SIR model more realistic, we developed an agent-based random walk model to test if SN is the most likely seed to initiate the propagation of misfolded alpha-syn. [pictures and illustrations]

B5) Identification of novel genetic risk variants for Alzheimer's disease in the HMGCR gene locus.

Nilsson IV. N.*, Picard, C., and Poirier, J.

Background: Cholesterol lowering drugs inhibiting HMG-CoA reductase activity (statins) have been found to be protective in retrospective analyses of sporadic AD. Recently, a genetic variant in the HMGCR gene, also associated with reduced reductase activity, was found to be protective in AD (Leduc et al., 2015). This led us to systematically investigate all the genetic polymorphisms at the HMGCR locus with a population frequency greater than 5%, and their relationship to AD risk and HMGCR expression. Methods: Whole-genome sequencing, plasma, and cerebrospinal fluid (CSF) biomarker data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). Genetic polymorphisms in and around the HMGCR gene were extracted, and logistic regressions were performed in plink (pngu.mgh.harvard.edu) to identify variants associated with either risk or protection. Further analyses were performed in SPSS; Kaplan-Meier for conversion rate analysis, ANCOVA for expression analysis and Mann-Whitney U test for CSF biomarker analyses.

Results: We identified three new single nucleotide polymorphisms (SNPs) associated with marked increased risk of AD (ORs = 2.4 - 2.7, ps < 0.05), however only in subjects also positive for APOE4 allele. Survival analysis further revealed that carriers of the risk alleles exhibit an accelerated conversion rate, but again only in APOE4 carriers (?2s > 6.6, ps < 0.01). HMGCR risk alleles were also associated with an increased gene expression in peripheral lymphocytes (Fs > 6.7, ps < 0.01); with no interaction with APOE4 status. Finally, a significant increase in CSF phospho-tau/tau ratio was observed in carriers of the risk alleles, particularly in APOE4 positive females (Us = 245.5, ps = 0.017), but not for A? levels.

Conclusions: We have identified three new SNPs in the HMGCR locus associated with risk of AD, accelerated conversion rate to AD, and increased CSF phospho-tau/tau ratio, specifically in APOE4 carriers. In line with our hypothesis that protection is mediated by reduction in HMG-CoA reductase activity, the identified risk alleles were shown to be significantly associated with increased HMGCR expression. We are now in the process of replicating these findings in an independent cohort composed of autopsy-confirmed AD cases and age-matched controls from a population isolate from eastern Canada.

B6) Slik is required cell-autonomously for regulating photoreceptor axon guidance in the Drosophila visual system.

Zahiremami*, M., Hsieh, HH., Chang W-T., and Rao, Y.

The fruit fly visual system is an excellent model to study the formation and function of neural circuits, given the numerous architectural similarities between the visual system of Drosophila and vertebrates at molecular, cellular, and network levels. Our lab has recently identified a novel mechanism by which Semaphorin-1a (Sema1a) reverse signaling upregulates axon-axon attraction in the developing Drosophila visual system. Sema1a promotes phosphorylation and activation of Moesin (Moe), a member of the ezrin/ radixin/ moesin family of proteins. Moe in turn downregulates the level of active Rho1 in photoreceptor axons leading to the upregulation of Fas2 mediated axon-axon attraction. To determine the mechanisms by which Sema1a promotes the phosphorylation of Moe, we tested candidate genes for interacting with Sema1a in regulating Moe. We found that Slik, a Ser/Thr kinase expressed in photoreceptor cells, interacts genetically with Sema1a and Moe in regulating axon-axon association. We then performed eye-specific genetic mosaic analysis and demonstrated that slik is required cell-autonomously in R1-R6 axon-axon association. To further determine how slik acts in the Sema1a reverse signaling pathway, we examined the effects of manipulating the levels of Slik on Fas2-mediated cell aggregation. The results show that Slik, like Sema1a, enhances Fas2 adhesive function. To further elucidate the Sema1a signaling pathway, we are currently investigating the potential physical interaction between Slik and Sema1a. The results will be presented at the meeting.

B7) Oligodendrocyte mitochondria are regulated by netrin-1

Diane S. Nakamura*, Damla Khan, Heidi M. McBride, Jack P. Antel, Timothy E. Kennedy

The form and function of axonal mitochondria have been well described; however, the presence of mitochondria in the oligodendroglial myelin sheath has only recently been reported. Mitochondria produce ATP and carbon chain backbones that are essential for the synthesis of lipids and myelin but little is known about how mitochondrial function is regulated in oligodendrocytes. Here we show that mitochondrial dynamics in oligodendrocytes are regulated by the secreted extracellular protein netrin-1. Netrin-1 and netrin receptors are enriched at oligodendroglial paranodal junction in the CNS and loss of netrin-1 or DCC function destabilizes myelin. We show that bath application of netrin-1 rapidly induces hyper-elongation of mitochondria while inhibition of a downstream signaling pathway results in severe mitochondrial fragmentation. Longer-term exposure to netrin-1 results in a decrease in OXPHOS and an increase in glycolysis in oligodendrocytes. Furthermore, we show that mitochondria are recruited to, and remain aggregated at, a local source of netrin-1. Using super-resolution structured illumination microscopy (SIM), we resolve mitochondria and a mitochondrial docking protein at the surface of netrin-1 coated beads. These findings demonstrate the regulation of mitochondrial fusion, fission, migration; and cellular respiration in oligodendrocytes by netrin-1. Our ongoing studies are investigating the specific signalling pathway downstream of netrin-1 regulation of mitochondrial dynamics in oligodendrocytes.

B8) A role for the calcium-activated protease calpain in the regulation of netrin-1/DCC-mediated cortical axon outgrowth

Philippe M. Duquette*, Doo Soon Im, David A Park, and Nathalie Lamarche-Vane

During embryonic development, neurons extend axons towards their appropriate synaptic targets to establish functional neuronal circuits. The growth cone, a highly motile structure at the axon tip, is capable of recognizing extracellular guidance cues and translating them into directed axon outgrowth through modulation of the actin cytoskeleton. The netrin family of guidance cues is vital for proper neuronal pathfinding. In particular, netrin-1 mediates its attractive function through the receptor deleted in colorectal cancer (DCC), which recruits proteins to mediate axon outgrowth and guidance. The calpain family of cysteine proteases is well known for its role in cleaving cystoskeletal proteins leading to cell death while playing a vital role in adhesion turnover during cell migration. Less is known about its role during brain development although some studies have highlighted its importance in the formation and maintenance of dendritic spines, and axon outgrowth. Here we identified DCC as a novel calpain substrate and we analyzed its role in the netrin-1/DCC signaling pathway during axon outgrowth. We found that calpain was able to cleave DCC in vitro. Calpain proteolysis of cytoskeletal targets is a mechanism of regulation of neurite consolidation and protrusive activity in neurons. We assessed calpain-specific spectrin cleavage, and found that netrin-1 activated calpain in embryonic cortical neurons in an Erk1/2-dependent manner. Furthermore, we demonstrated that netrin-1 stimulation promoted cleavage of DCC within the same time-frame of calpain and ERK1/2 activation. Interestingly, netrin-1-mediated Erk1/2 activation was abolished in calpain-1/2-deficient cortical neurons dissociated from Nestin-Cre;Capns1fl/fl embryos compared to control neurons. However, DCC expression was not unaffected in calpain-deficient cortical neurons. Using another calpain-specific substrate t-BOC that links calpain activity to fluorescence intensity in live cortical neurons, we showed that netrin-1 stimulated calpain activity in live cortical neurons. Interestingly, cortical neurons overexpressing calpastatin displayed longer neurites. Using an siRNA approach to diminish both calpain-1 and calpain-2 expression, neurons with reduced calpain expression also displayed longer axons and were unresponsive to netrin-1 stimulation. Altogether, we propose a novel model whereby netrin-1/DCC-mediated axon outgrowth is modulated by calpain-mediated proteolysis of DCC and cytoskeletal targets.

B9) Bound and GAGed: Molecular Mechanisms Localizing Netrin-1 in Neural ECM

Stephanie N. Harris*, Heleen M. van 't-Spijker, Celina Cheung, K.Adam Baker, Simon Moore, James W. Fawcett, Timothy E. Kennedy

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

B10) Synchronizing to the beat in adults with a stutter: behavior and functional imaging data

Anastasia G. Sares*, Mickael Deroche, Hiroki Ohashi, Douglas M. Shiller, Vincent Gracco

Sensorimotor integration is a hallmark of both music and speech production. It has been suggested that deficient sensorimotor integration is a primary trait of individuals who stutter. What is unclear is whether this apparent deficit extends to other, non-speech behaviors. Here we compare the performance and brain activity of adults who stutter (AS) and adult controls (AC) in a metronome synchronization task. During the experiment, participants squeezed on a pressure pad in time with an auditory metronome, which sometimes changed its speed. Synchronization accuracy during stable periods was examined, as well as the dynamics of recovering from a tempo change. Replicating previous studies, we found that participants squeezed slightly in advance of the auditory beat; however, the AS group was even further in advance than controls. AS were also less consistent than AC during slower tempi, and adjusted differently to slowing tempo changes. MRI analyses focused on cortical (premotor, supplementary motor) and subcortical (cerebellum, basal ganglia) areas associated with timing that are known to show different activation in AS and AC during fluent speech.

B11) Hippocampus Cross-Frequency Coupling is Associated with Seizure Activity in Mesial Temporal Lobe Epilepsy

Soheila Samiee, Maxime Levesque, Charles Behr, Massimo Avoli, Sylvain Baillet.

Cross-frequency coupling is a marker of interactions between neuronal sub-populations. Since such interaction can be altered in epilepsy, abnormal levels of coupling could provide a biomarker of epileptogenesis, and point at the pathophysiological mechanisms involved. In this study, we measured phase-amplitude coupling (PAC), a form of cross-frequency coupling between neural oscillations, in an animal model of mesial temporal lobe epilepsy. Sprague-Dawley rats (n = 4, 250-300 g) were injected with pilocarpine (360 mg/kg, i.p) to induce a status epilepticus (SE) that was stopped after 1 h with diazepam (5 mgkg, s.c.) and ketamine (50 mg/kg, s.c.). Control animals (n = 6) did not receive any treatment. Three days after SE, all animals were implanted with bipolar electrodes in the CA3 subfield of the hippocampus, the entorhinal cortex, the dentate gyrus and the subiculum. Continuous video/EEG recordings were collected 24/7 at a sampling rate of 2 kHz, over a period of 15 consecutive days. Pilocarpine-treated animals produced spontaneous seizures on average 6.7 days after SE. Control animals did not show any seizure. Analysis of PAC revealed that CA3, which was the seizure onset zone in most cases, was the only region that showed significantly stronger coupling in epileptic animals compared to controls. This strong coupling was between the phase of slow-wave oscillations (< 1 Hz) and the amplitude of fast rhythms in the gamma-ripple band (50 - 180 Hz). These fast oscillations mainly occurred at the transition between down and up states (ascending phase of the slow-wave oscillations). Our results further revealed that the averaged coupling strength in CA3 was positively correlated with the daily seizure count. These results were not biased by the occurrence of inter-ictal spikes, which was not modulated by the phase of the slow-wave oscillations. Altogether, these results indicate that during slow-wave sleep, the seizure onset zone expresses stronger phase-amplitude coupling between the slow cycles of excitability originating from the neocortex, and the local oscillatory bursts in the gamma-ripple band. Further, the modulation of this fast, transient activity is modulated by slow excitability cycles is stronger around seizure occurrences. We conclude by pointing at the potential of this new PAC as a signal marker of epileptogenesis, which may readily transfer to routine scalp recordings obtained in clinical units with EEG.

B12) Acute Infarction Mapping Indicates that the Telephone Interview for Cognitive Status Can Predict Memory Deficits One Year Following Ischemic Stroke

Melissa McSweeney*, Shyam Prabhakaran, & Joel L. Voss

The Telephone Inventory for Cognitive Status (TICS) is a brief screening instrument for cognitive impairments administered via telephone. It includes delayed recall, short-term recall, verbal, recent/semantic memory, orientation, and attention/calculation components. We mapped acute ischemic strokes to determine whether TICS subscores could be predicted based on acute infarct location, thus suggesting validity with respect to expected region-specific brain-behavior relationships. Ischemic stroke survivors (N=129) completed the TICS one year after discharge. Voxel-based lesion-symptom mapping suggested that infarcts of mesial temporal regions were marginally predictive of delayed recall, whereas no other subtests were related to infarct locations. We then inspected delayed recall scores in the subset of subjects with infarcts of the mesial temporal lobe (N=15). These subjects scored significantly lower than the rest of the cohort (mean=4.18 vs. 5.09; t=2.005, p=0.047), and subsequent analyses indicated that this was not secondary to lesion volume differences. This confirms the expected relationship between mesial temporal damage and lasting memory impairment. These findings suggest neurological validity of TICS delayed recall, as this was the only subtest reliably predicted by acute infarct location. Other TICS measures are either not strongly related to infarct location or weaknesses of our approach limited identification of these relationships.

B13) Resting-state functional connectivity of the basolateral amygdala is altered in pre-weaning rats subjected to chronic early life stress

*A. GUADAGNO, M. S. KANG, A. P. MATHIEU, E. GUMA, G. A. DEVENYI, P. ROSA-NETO, M. CHAKRAVARTY, C.-D. WALKER

Early-life stress (ELS) exposure has life-long consequences for both brain structure and function, and can ultimately impact cognitive and emotional behavior, increasing vulnerability to mental disorders. The basolateral amygdala (BLA) plays an important role in anxiety and fear conditioning and through its wide connections to the prefrontal cortex (PFC) and hippocampus (HIP) in particular, can affect stress reactivity and emotional behavior. However, how ELS affects amygdala function and connectivity in developing rats is unknown. We used the naturalistic limited bedding/nesting (LBN) paradigm to induce chronic stress in the pups between postnatal day (PND) 1-9. Normal bedding (NB) conditions were used as control. Sprague Dawley male NB or LBN rats received structural (FLASH, Resolution 0.1x0.1x0.1mm, TA 23 min) and resting-state functional MRI (rs-fMRI, RAREst, Resolution 0.25x0.25x0.8mm, TR/TE 3000/28 ms, TA 5 min) under <2% isoflurane anesthesia on PND18. All scans were obtained on a Bruker 7T MRI (650 mT/m in 150μs) 24 hrs after treatment with Manganese Chloride (MnCl2, 32 mg/kg, sc), an MRI contrast agent. Three rs-fMRI acquisitions for each animal were preprocessed and registered to a group average anatomical image (FLASH). Each run then generated connectivity maps based on four BLA seeds (left, right, anterior and posterior) using FMRISTATS. The individual connectivity maps were transformed into the template space. All three runs were combined to build a subject level connectivity map. The final results were corrected for multiple comparison using Random Field Theory, $p = 0.05$. Significantly enhanced contralateral PFC connectivity was found in LBN compared to NB pups from both Left BLA seeds, but only from the Right Posterior BLA. Animals subjected to LBN rearing also exhibited increased connectivity from both Posterior BLA seeds to the contralateral HIP. The ipsilateral connectivity to the HIP was only increased in the Right Posterior BLA, while the Anterior BLA networks tended to show reduced connectivity to the HIP. LBN pups showed greater Left BLA connectivity to the paraventricular nucleus and to the insular cortex. In summary, ELS enhanced BLA-PFC/Hip and insula connectivity in immature preweaning pups with a strong contralateral component. Increased connectivity in these critical nodes of the emotion processing network in developing rats might underlie enhanced fear conditioning and anxiety observed in ELS-exposed adults. Furthermore, most structures displaying enhanced connectivity after ELS are also part of the extended stress circuitry that is recruited under chronic stress in adult animals.

B14) Moving away from single AD-signature ROI: Assessing the relationship between whole-brain gray matter pattern, AD pathology, and cognition in healthy elderly at risk of AD

Alexa Pichet Binette*, Etienne Vachon-Presseau, Renaud La Joie, Judes Poirier, Pedro Rosa-Neto, Louis Collins, John Breitner, Sylvia Villeneuve, PREVENT-AD Research Group

Background: Hippocampal volume (HV) is often used to indicate neurodegeneration in Alzheimer's disease (AD) (Sperling et al., 2011). Hippocampal atrophy is not specific to AD, however (Bartsch & Wulff, 2015), and we investigated whether whole-brain (wb) gray matter (GM) pattern is better related to CSF biomarkers of AD or cognition than single metrics such as HV.

Methods: We obtained structural MR images from 296 members of the PREVENT-AD cohort of cognitively normal adults with a parental or multiple-sibling history of AD dementia (mean age=64). We compared these with reference groups of 198 young individuals from the Cambridge dataset and 270 from the Human Connectome Project (both aged 35), as well as cognitively impaired ADNI participants (50 with early MCI, 65 with late MCI, and 72 with AD dementia (mean age 74)). We derived 24 GM regions of interest (ROI) from an independent components analysis across all groups. Next, we assessed the mean GM density in all ROI separately for each reference group. Then, for each PREVENT-AD participant, we correlated the ROI-specific GM density pattern vs. that among the reference groups (Figure 1). We evaluated HV using patch-based segmentation (Coupé et al., 2011). Finally, we used general linear models to examine if the wbGM pattern similarity of each PREVENT-AD participant with the corresponding pattern of the reference groups, the HV, or individual ROIs, was associated with CSF Abeta42 and p-tau levels, as well as cognitive domain scores on the RBANS.

Results: The wbGM pattern metrics, but not individual ROIs GM or HV, were associated with CSF biomarkers and cognition. A wbGM pattern similar to that of the young groups was related to better immediate memory, language and attention (all $p = 0.03$), while a pattern similar to the cognitively impaired groups was associated with increased amyloid burden ($p < 0.05$, Table 1).

Conclusions: In healthy elderly with a family history of AD, wbGM pattern appears more potent as a predictor of cognitive performance and amyloid burden than HV or individual ROI metrics. Evaluation of whole-brain structural changes may therefore hold particular interest for early identification of AD in those at risk.

B15) Striatal Morphometric Alterations in *DCC* Haploinsufficient Humans and Mice

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Introduction: We have reported that a mutation of the axon guidance molecule receptor gene, *DCC*, decreases midbrain to striatal connectivity in humans (Vosberg et al *CCNP* 2017) and both midbrain to nucleus accumbens (NAcc) dopamine innervation (Reynolds et al *Biol Psychiatry* 2017) and dopamine release (Grant et al *Eur J Neurosci* 2007) in mice. Here, we tested whether these changes might be associated with alterations in striatal volume, as measured in a translational cross-species magnetic resonance imaging (MRI) study.

Methods: Automated morphometric analyses were conducted in mice and humans haploinsufficient for *DCC* (+/-). In mice, a 7 Tesla MRI scanner was used to characterize volumetric differences between $DCC^{+/-}$ (n = 11) and wildtype (n = 16) mice in adolescence (postnatal day 33±2) and again, in the same animals, in adulthood (postnatal day 75±15). In humans, a 3T MRI scanner was used to acquire anatomical scans from members of a Quebec family, 18 of whom are $DCC^{+/-}$ and 12 of whom are $DCC^{+/+}$, as well as from 19 unrelated healthy controls.

Results: In humans, whole-brain corrected effects among $DCC^{+/-}$ carriers identified reduced putamen volumes, relative to controls. Strikingly similar reductions in NAcc volumes were evident in $DCC^{+/-}$ mice, compared to wildtype littermates, and these effects were present both in adolescence and in adulthood.

Conclusion: The results add to the evidence that DCC affects development within the dopamine-innervated striatum, and that these effects occur in both mice and humans. These effects might not be restricted to rare mutations. Indeed, a recent large genome-wide association study in the general population (n=30,717) found that putamen volume was influenced by four genes including a single nucleotide polymorphism of *DCC* (Hibar et al *Nature* 2015). The present translational study strengthens the evidence for this effect in an *a priori* hypothesis guided investigation of striatal volume.

B16) Environmental programming of adult foraging behavior in the nematode Caenorhabditis elegans

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Environmental influences during development can have long-term effects on adult physiology and behavior. Adverse environmental conditions during early development have been linked to a number of adult-onset metabolic and psychiatric disorders. The short life-cycle, genetic tractability and the anatomical simplicity of the neuronal network makes the nematode Caenorhabditis elegans an ideal model organism to study environmental programming of adult behavior. Here we investigate how starvation at early larval stages affects developmental plasticity and alters adult behavioral traits. In response to starvation, C. elegans larvae may enter an arrested developmental stage, called dauer. We examined if the characteristic foraging behavior seen in C. elegans adults are changed in animals which experienced dauer in their developmental history. We established that post-dauer animals show reduced exploratory foraging behavior. This behavioral plasticity in response to early life stress is seen in wild isolates but not in the lab-adapted strain. Our current studies are exploring the neural correlates of this permanent change in behavior using calcium imaging. Initial findings indicate that dynamics of the interneuron circuitry regulating reversals in an animal's trajectory is altered in post-dauers. Since nematodes share conserved genetic, metabolic and developmental pathways with mammals, this work will add to our understanding of developmental plasticity in response to environmental stress.

B17) Recessive Mutations in *NDUFA2* Cause Mitochondrial Leukoencephalopathy

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Objective: Deficiencies of the mitochondrial respiratory chain complex I frequently result in leukoencephalopathy in young patients, and different mutations in the genes encoding its subunits are still being uncovered. *NDUFA2* encodes an accessory subunit of complex I, and currently only one patient with Leigh disease has been reported with recessive mutations in this gene. Here, we report two patients with a different phenotype including cystic leukoencephalopathy and recessive mutations in *NDUFA2*.

Methods: Whole exome sequencing (WES) was performed on a subset of patients with suspected mitochondrial leukoencephalopathy due to complex I deficiency. Two patients were identified with mutations in *NDUFA2* and biochemical studies were performed on patient fibroblasts. Patient charts and brain MRIs were reviewed.

Results: Patient 1 was known for carnitine transporter deficiency due to recessive mutations in *SLC22A5*, but exhibited an atypical clinical course for this disorder, and most importantly, had a cystic leukoencephalopathy suggestive of complex I deficiency on brain MRI. WES revealed a homozygous mutation in *NDUFA2* (c.134A>C, p.Lys45Thr), and complex I deficiency was confirmed through biochemical analysis. Patient 2 presented with developmental regression, and a cystic leukoencephalopathy was documented on brain MRI. Compound heterozygous variants were found in *NDUFA2* (c.134A>C, p.Lys45Thr; c.225del, p.Thr75fs5*).

Conclusion: Our work demonstrates that recessive mutations in *NDUFA2* can cause cystic leukoencephalopathy. Additionally, the first patient presented here teaches a good clinical lesson: when the clinical phenotype does not fit the diagnosis, one cannot assume to a broadened phenotype but rather, a second diagnosis should be considered and investigated.

B18) Using Localized Markov Random Fields to Improve Multi-Atlas Label Fusion on Multi-Label Datasets

Charles Lagace*, Gabriel A. Devenyi, Nikhil Bhagwat, M. Mallar Chakravarty and Alzheimer's Disease Neuroimaging Initiative

Automated algorithms that can identify neuroanatomical regions in magnetic resonance images (MRI) enable large-scale analyses of brain morphometry. A well-documented method for automated segmentation is multi-atlas registration, which produces many candidate labels and then performs label fusion. Recently, our group developed Autocorrecting Walks over Localized Markov Random Fields (AWoL-MRF) for label fusion [1]. However, this method was designed for label sets containing a single label. We implemented Multilabel AWoL-MRF (M-AWoL-MRF), a new algorithm inspired by AWoL-MRF which can perform label fusion on multi-label data sets. The algorithm exploits local intensity profiles and label neighbourhoods to produce new probability estimates for each label on a voxel-wise basis. We compared M-AWoL-MRF to majority vote and AWoL-MRF in two separate data sets: the first-episode psychosis (FEP) multi-label data set [2], and the Alzheimer's Disease Neuroimaging Initiative (ADNI) single-label data set [3;4]. For each data set, the performance of each algorithm is evaluated using the Dice similarity coefficient, and the gold-standard is the manual segmentation. On the FEP data set, M-AWoL-MRF surpasses majority vote with a maximum Dice score of 0.915. On the ADNI data set, the Dice score of M-AWoL-MRF peaks at 0.882, which is superior to majority vote and comparable to AWoL-MRF.

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B19) Effects of dopamine depletion on signal variability and functional connectivity of resting state brain networks

Golia Shafiei*, Yashar Zeighami, Alain Dagher, Bratislav Misic

Dopaminergic projections are hypothesized to stabilize neural signaling and neural representations, but their role in shaping local information processing and large-scale network interactions remains unclear. Here we investigate the effects of lowered dopamine levels on functional connectivity and signal variability of the healthy brain at rest. Acute phenylalanine and tyrosine depletion (APTD) technique was used to induce dopamine depletion in 51 healthy participants who underwent high-resolution resting-state functional MRI (fMRI). Functional data were parceled into 83 cortical and subcortical areas using the Desikan-Killiany atlas, and then further subdivided into 1015 approximately equally sized parcels. Functional connectivity was estimated as a Pearson correlation coefficient between regional time series. Sample entropy (SE) analysis was used to estimate regional signal variability by quantifying the similarity of any two sequences of data points in the fMRI time series. Multivariate partial least squares (PLS) analysis was used to statistically assess changes in signal variability before and after dopamine depletion. PLS results in a set of latent variables (LV), that are weighted combinations of experiment design (i.e. a contrast) and signal variability patterns that optimally covary with each other. We found one significant latent variable (permuted $p \sim 0$, accounting for almost 100% of covariance), capturing a pattern of increased signal variability following dopamine depletion. The pattern was spatially diffuse, but most pronounced in areas associated with the somatomotor and salience resting-state networks. Finally, changes in signal variability were concomitant with changes in functional connectivity, such that nodes with the greatest increase in signal variability following dopamine depletion also experienced the greatest decrease in functional connectivity. Our data suggest that dopamine may act to stabilize neural signaling, particularly in areas related to somatomotor function and orienting attention towards behaviorally-relevant stimuli. Moreover, dopamine-dependent signal variability is critically associated with the functional embedding of individual areas in large-scale networks.

B20) Molecular Mechanisms Involved in Incomplete Neural Cell Differentiation in Glioblastoma

Lawrie Shahbazian*, Rita Lo, Stefano Stifani

Background: Glioblastoma multiforme (GBM) is the most common malignant primary adult brain tumor. GBM is associated with a poor patient survival of about 15 months. This is due to the near inevitable recurrence of the tumor despite surgical removal combined with adjuvant chemotherapy and radiation therapy. Recurrence is hypothesized to arise from stem-like cells with brain tumor initiating ability cells thought to be capable of evading the current therapies. Hereafter, these cells will be referred to as brain tumour initiating cells (BTICs). In this regard, we aim to investigate the mechanisms underlying the ability of BTICs to maintain an undifferentiated neural phenotype.

Hypothesis: We hypothesize that BTICs are unable to progress to a differentiated phenotype due to deregulated mechanisms that normally control the balance between the undifferentiated and differentiated states. Previous work in the lab has shown that the RUNX:CBFB transcription factor complex, known to be involved in the regulation of cell proliferation and differentiation in the healthy nervous system, is abnormally upregulated in GBM and that this upregulation is correlated with worse overall survival. Consistent with this observation, RUNX:CBFB is highly expressed in several patient-derived BTIC lines maintained under conditions promoting selfrenewal and proliferation. Based on these observations, we postulate that RUNX:CBFB may contribute to mechanisms involved in the maintenance of the undifferentiated state in BTICs.

Methods & Results: To characterize the involvement of RUNX:CBFB in BTICs we characterized the behavior of several patient-derived BTIC lines under conditions promoting either maintenance of the undifferentiated state or progression toward a more differentiated phenotype. Our studies showed that BTIC culture under “differentiative” conditions leads to a down-regulation of neural stem/progenitor cell markers and upregulation of neuronal and astroglial markers. Moreover, we observed that acquisition of more differentiated neural phenotypes is correlated with down-regulation of endogenous RUNX:CBFB protein levels in BTICs. More importantly, our studies provided evidence suggesting that impairment of RUNX:CBFB, using pharmacological inhibition and shRNA-mediated knockdown studies, under “non-differentiative” conditions mimics at least in part some of the phenotypic changes observed after BTIC exposure to differentiative conditions.

Conclusion: These experiments revealed that, under appropriate culture conditions, BTICs can progress towards more astroglial and more neuronal phenotypes and similar responses can be observed after RUNX:CBFB impairment. We therefore suggest that RUNX:CBFB upregulation in GBM cells contribute to the mechanisms that allow cells maintain a more stem-like state by inhibiting programs of neuronal and astroglial differentiation. This findings provide information on the molecular mechanisms underlying the pathobiology of cancer cells in GBM

B21) Identifying the neuronal Aβ-immunopositive pool within the human hippocampus

Lindsay A. Welikovitch*, Ethan Yang, Sonia Do Carmo, Pierre Chaurand, A. Claudio Cuello

Background: The established neuropathological features of Alzheimers disease (AD) include the presence of extracellular amyloid-β (Aβ) plaques within the brain. Despite the fact that the AD-neuropathology is typically studied in already-diagnosed patients, it is now apparent that these neuropathological events evolve silently for decades before symptom-onset. Indeed it has been shown by our lab and others that Aβ first accumulates intraneuronally (iAβ) before the appearance of extracellular plaques both in humans and animal models of AD. Despite its apparent intraneuronal localization early in the disease-process, studying the occurrence and pathological relevance of iAβ has been confounded by much controversial debate: antibodies targeting Aβ peptides typically show specificity for the amyloid precursor protein (APP), which is physiologically abundant within the intraneuronal space. High-resolution fluorescent microscopy imaging of human brain material is made especially difficult by the presence of auto-fluorescent lipofuscin, which occludes the detection of true immunoreactive sites.

Methods: To detect intraneuronal Aβ and APP, human hippocampal tissue from control subjects was probed using highly specific Aβ- and APP-directed antibodies, McSA1 and pab27576 respectively, and imaged by high-resolution confocal microscopy and super-resolution structured illumination microscopy. To measure the extent of co-colocalization between neuronal Aβ- and APP-immunoreactive sites, Manders and Pearson's coefficients were calculated using ImageJ-image analysis. Antibody specificity was then tested by peptide-adsorption and MALDI-mass spectrometry.

Results: We show that neurons within the control human hippocampus carry appreciable amounts of detectable intraneuronal Aβ-immunoreactive material, and that these immunoreactive sites are distinguishable from those associated with APP; indeed, co-localization analysis revealed that over 90% of Aβ-immunoreactive sites are spatially distinct from those associated with APP. The specificity of the antibodies used was verified by immunohistochemistry following peptide-adsorption as well as MALDI-mass spectrometry analysis.

Conclusions: Our results definitively reveal the presence of an Aβ-immunopositive pool within the neuronal space, which is spatially distinct from that associated with APP. These results validate the physiological occurrence of the intraneuronal Aβ species, implicating the toxic intracellular material as an early feature of the asymptomatic phase of AD.

B22) Predictive coding during natural speech listening studied using MEG and recurrent neural networks

Peter Donhauser*, Maryse Thomas, Benjamin Morillon, Vincent Gracco, Sylvain Baillet

Cortical processing along hierarchical sensory pathways has been described as a continuous interplay between 'top-down' predictions and 'bottom-up' propagation of prediction errors or surprise. There is evidence that there are separate oscillatory 'channels' for bottom-up (theta, gamma) and top-down (alpha, beta) information flow. Since these models are usually tested using artificial experimental stimuli as e.g. pitch sequences or word-by-word visual presentation of sentences, here we want to test whether predictive coding and its oscillatory correlates can model continuous cortical processing during naturalistic speech listening. Since auditory input in speech fluctuates at phrasal and syllabic rhythms within the neural delta and theta bands, we expect neural activity in this frequency range to be linearly coupled to the auditory information, whereas activity in the alpha to gamma range will be modulated in amplitude (AM). In study 1, we show this dissociation between low-frequency linear coupling and high-frequency AM. In study 2, we develop a novel approach to study the influence of predictions (quantified by surprise and entropy) on continuous neural activity using a combination of deep neural language models to analyze stimulus predictability and multivariate temporal response functions to link this to continuous MEG signals during naturalistic listening. We show consistently across subjects an enhancement of the (linear) response at 100 ms by high surprise, which is faster than what was previously found using word-by-word presentation. The higher frequency amplitude modulation results show effects in the alpha/beta range that build up already before the auditory input, suggesting that they reflect top-down "predictions."

B23) Learning the whole from understanding its parts: In Vivo, Multimodal Parcellation of the Thalamus

Anthony G. Chen*, Raihaan Patel, Christopher Steele, Sejal Patel, Jurgen Germann, Christine Tardif, Gabriel A. Devenyi, M. Mallar Chakravarty

Can a whole be described as the sum of its parts? Brain parcellation - the act of dividing the brain into sub-regions - has intrigued neuroanatomists since the dawn of the discipline. Here, we explore a de novo way of parcellating the thalamus - a subcortical structure and neuroanatomical hub essential for information relay and integration [1]. We employ Non-Negative Matrix Factorization (NMF) - a data-driven technique previously shown to be applicable in compartmentalizing brain structures [2; 3]. Unlike most parcellation methods, which rely on a single type of information, NMF allows for the decomposition of high dimensional, multi-modal data into components that capture patterns of covariance . The nonnegative constraint is also sensible for biological image data, and results in a parts-based, additive representation of the original images that is highly interpretable [4; 5]. Being completely data-driven, NMF is generalizable to both different brain structures and types of data. We use structural and diffusion data from the Human Connectome Project (T1-weighted, T2-weighted, mean diffusivity, fractional anisotropy) [6]. Results show NMF produces spatially continuous components with varying microstructural properties, in line with previous knowledge regarding thalamic substructures. The dependency of voxels on each components is used as a reduced-dimension representation of the data for k-means clustering, generating discrete parcel boundaries. A preliminary probability-based tractography analysis show connectivity from individual parcels to distinctive cortical areas.

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B24) PTSD: Decreased Locus Coeruleus Noradrenergic Activity Modulates Resilience to Stress

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Background: Post-traumatic stress disorder (PTSD) is a debilitating disorder and affects 8% of Americans. It is caused by exposure to extreme stress and is generally characterised by intrusive fear-related memories, hyper-arousal, avoidance and negative feelings. Interestingly, most individuals exposed to extreme stress, do not develop PTSD and are considered resilient and males appear to be more resilient to stress compared to females. Researchers have placed intense interest in understanding the neural basis of resilience to stress. The noradrenergic system is thought to play a key role in the regulation of stress responses and it has been proposed that the locus coeruleus (LC) may play a modulatory role in resilience to stress.

Methods: In the present study, we investigate the role of the LC in susceptibility and resilience extreme stress using the learned helplessness mouse model which produces two behavioural phenotypes: helpless mice that are susceptible to stress and non-helpless mice that are resilient to stress. We compared male and female VMAT2DBHcre KO mice which are depleted of noradrenaline transmission to wild-type mice. We measured the activity of noradrenergic locus coeruleus neurones using in vivo electrophysiological recording in WT controls, helpless and non-helpless mice.

Results: We found that stress exposure provoked different behavioural phenotypes in females and males and that depletion of noradrenaline transmission alleviated helpless behaviour in both males and female mice. Furthermore, in-vivo electrophysiological recordings of LC noradrenergic neurons showed a decrease of bursting activity in noradrenergic LC neurons in non-helpless mice compared to helpless and control mice.

Conclusion: Taken together, these findings suggest that the noradrenergic system plays a different modulatory role in males and females in resilience to stress and that decreased LC activity results in non-helpless behaviour.

B25) Identifying new effectors of the EphB2 cascade through evaluation of ephrin-B2:EphB2 forward signalling assays.

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Ephrin-B:EphB forward signalling plays a vital role in many tissues during development, including in the guidance of spinal motor axons. However, some aspects of the molecular cascade downstream of EphB receptors remain mysterious. To explore these gaps in our knowledge, we conducted a BioID experiment followed by mass spectrometry analysis to identify proximal protein candidates for EphB2. We used a stable HEK293 cell line expressing an inducible EphB2-BirA*-Flag construct and exposed cultures to ephrin-B2 or control ligands. We performed four replica experiments, and identified hundreds of proteins preferentially recruited or removed from the vicinity of EphB2 upon ephrin-B2 stimulation, compared with the control conditions. After performing extensive literature review on the candidates, we performed in situ hybridization experiments on chick embryonic spinal cord sections to assess whether the most promising genes were expressed in spinal motor neurons. We narrowed down our candidate selection to 10 proteins. Moving forward, these candidates will be knocked-down (KD) in spinal cords and cell lines using the CRISPR-Cas9 system, through in ovo electroporation and transfection, respectively. Once KD is achieved, various ephrin-B2:EphB2 functional assays will be conducted to characterise whether and how these candidates participate in the EphB2 forward signalling pathway. Three of these assays will involve making chick spinal cord explants with the KD tissue. First, a substrate preference assay with Fc (control) vs. eprhin-B2 stripes will reveal whether repulsion from the cue is abolished after candidate KD. Second, a growth cone collapse assay will allow us to evaluate whether this short-term response to ephrin-B2 stimulation is affected by the KD. Third, KD explants will be stained with anti-phospho Src (Y416) antibodies after ephrin-B2 exposure, in order to investigate whether this known forward signalling readout is compromised. Finally, transfection of the CRISPR constructs into HeLa cells will allow us to examine whether the cytoskeletal collapse response to ephrin-B2 is affected by candidate KD. By using these four assays, we will be able to characterise the role these novel candidate effectors play in ephrin-B2: EphB2 forward signalling.

B26) Impact of cholinergic atrophy in the progression of Alzheimer's disease

Chiara Orciani*, Rowan Pentz, Hélène Hall, Claudio Cuello

Cholinergic therapies are commonly prescribed to Alzheimer's disease (AD) patients for their ability to transiently relieve cognitive symptoms. However, recent evidence showing that the use an acetylcholinesterase inhibitor can reduce brain atrophy suggests that cholinergic treatments could have disease-modifying effects. Mechanistic insight into this phenomenon is given by the discovery of a trophic interdependency between the cortex and cholinergic output nuclei in the basal forebrain (BFCNs). Cholinergic neurons of the BFCN depend on a retrograde supply of cortical NGF for the maintenance of their function and phenotype. Cholinergic signalling through muscarinic receptors has trophic effects and, in the context of AD, can switch APP processing towards a non-amyloidogenic pathway. Given that the NGF metabolic pathway is disrupted in AD (Bruno et al., 2009) and that amyloid oligomers are sufficient to induce such disruptions, we hypothesize that there is a feed-forward pathological cycle in AD in which increasing amyloidosis disrupts NGF metabolism leading to the trophy of the BFCN, and the lack of output from the BFCN leads to atrophy and increased produced of amyloid in the cortex (Iulita and Cuello, 2014, 2016). To test the above hypothesis we will selectively immune-deplete the cholinergic neurons of the nucleus basalis (which provides the large majority of cortical cholinergic synapses in rodents and their sum total in humans) in McGill-R-Thy1-APP rats, a model of Alzheimer's-like amyloid pathology. Using Western Blotting, ELISA, qPCR, and immunohistochemistry, we will subsequently assess cohorts of rats at 2, 7 and 16 months post-immunolesion to determine whether the cholinergic depletion leads to an acceleration of amyloid pathology, an acceleration of NGF metabolic dysregulation, and atrophism of cortical cells. We have already defined the stereotaxic coordinates to target the nucleus basalis with the 192-IgG-Saporotoxin. The next steps will be the injection of different concentrations of 192-IgG-Sap to define the amount of toxin required to produce a thorough, selective immunolesion. This study could have fundamental importance for understanding the relationship between AD-like amyloid pathology, NGF metabolism, and the status of basal forebrain cholinergic neurons with important implications for future therapeutic avenues.

B27) Sonic hedgehog guides axons through release of an Elmo-Dock complex

*Shirin Makihara, Steves Morin, Jean-Francois Cote, Patricia T. Yam, Frederic Charron

In the developing spinal cord, Sonic hedgehog (Shh) attracts commissural axons toward the floorplate. How Shh regulates changes in the growth cone cytoskeleton, in particular, the guanine nucleotide exchange factor (GEF) acting downstream of Shh, remains unknown. We found that Shh activation of the RhoGTPase Rac1 required the activity of Dock, an unconventional Rho GEF. Knockdown of Dock3 and 4, or its binding partner Elmo1 and 2, abolished commissural axon attraction by Shh in vitro. Importantly, Dock and Elmo activity were also required for correct commissural axon guidance in vivo. We show that Dock and Elmo interact with Boc, the Shh receptor, and that this interaction is reduced upon stimulation with Shh. Furthermore, Shh stimulation translocates Elmo to the growth cone periphery. Based on these results, we propose a model where Shh stimulation releases the Dock/Elmo complex from Boc, thus allowing Dock/Elmo to regulate RhoGTPase activity in axon guidance. These results reveal how Shh can modulate cytoskeletal reorganization in growth cones and identify new mediators of non-canonical Shh signaling.

B28) The protoSPACE Map: prototypical Spatial Patterns of Activation from Common Experience

Zhang*, A., Proulx, S., Chen, Y., Akhavein, H., & Farivar, R.

Whether our brains operate in the same manner remains a persistent question in neuroscience. Previous studies have shown that subjects viewing the same movie exhibit widespread spatiotemporal correlation during functional magnetic resonance imaging (fMRI). However, previous studies have not considered that the visual system fires in spatial patterns, a feature integral to its complexity. In the current study, we investigated spatial pattern similarity between subjects during movie viewing. We will produce a prototypical map of the visual system, demonstrating which areas of the brain process visual stimuli the same way in different people. Unlike previous studies, we used 3-D movies to maximize realism and clips that minimize narrative to focus on visual processing. Fifty-six subjects watched two 5-minute movie clips from a 3-D movie during an fMRI scan. We calculated the between-subject spatial pattern correlation centered on every voxel of the posterior brain during the clips. High correlation at a voxel means that the space surrounding that voxel has a spatial pattern that looks extremely similar across subjects. A single threshold permutations test was used to test for significance. We found significant spatial correlations between subjects in the majority of early visual cortex, as well as higher visual areas. Our results show that early visual cortex processes information the same way in different people, thereby answering one aspect of the question of whether different brains operate in the same manner.

B29) In-vitro modeling of electrode-tissue parameters

*Maran Ma, Timothy Kennedy

The long-term causes underlying the failure of neural recording electrodes is an active question in the community of neural implant users and developers. It is known that a variety of phenomena contribute to signal degradation, but to engineer better devices, the impact of each factor must be quantified and prioritized. Excluding modes of general implant failure such as connectors and meningeal responses, the causes of gradual loss of signal fidelity on individual electrodes include: 1) insulation breakdown, 2) biofouling, 3) glial ensheathment, and 4) neuronal death. One challenge to teasing these factors apart is that they occur simultaneously in-vivo. Another is that impedance, the primary method of monitoring electrode status, is affected by multiple factors. The purpose of this project is to build a simple and cost effective in-vitro setup that models each phenomenon separately. We then aim to use this system to quantify the impact of each electrode-tissue condition on impedance spectra and signal quality.

B30) **Investigating the Functional Recovery Patterns of Neural Networks Following Prolonged Anesthetization Using Multivariate Partial Least Squares Analysis**

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The functional recovery of neurological networks following anesthesia-induced unconsciousness has recently been investigated using neurophysiological data. However, these studies do not effectively model the brain's recovery from general anesthesia used in major surgery, as they involve protocols that either just cross the threshold of unconsciousness, or that induce profound unresponsiveness for a brief period. Furthermore, topological network changes have not been studied beyond the initial recovery of consciousness. To study the functional recovery of neural networks associated with the the recovery of cognitive functions following prolonged anesthetization, we recorded high-density EEG from 9 health participants using a clinically-relevant anesthetic protocol. Participants were anesthetized for 3-hours and measures of cognitive functioning were recorded at baseline, and at 30-minute intervals for three hours following recovery of consciousness. During each recording session, subjects performed a cognitive test battery consisting of 6 subtasks. Brain networks for each subtask and each session were constructed using Phase Lag Index (PLI) - a measure of functional connectivity. Multivariate partial least squares analysis was applied to these brain networks to investigate significant changes in network level functional connectivity throughout recovery. A significant increase in network connectivity was observed upon recovery of consciousness across all 6 of the cognitive tasks. Furthermore, the networks driving the changes associated with each individual cognitive tasks were identified, and cross-referenced with known functions of localized brain regions. These results demonstrate the brain's time-evolving reconstruction of cognitive functioning following a major perturbation, and demonstrate the utility of Partial Lease Squares Analysis to identify physiological-relevant network changes in this situation.

B31) Role of neuromusculin in the formation of Drosophila melanogaster hardwired mechanosensory system

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Introduction: Cell surface molecules are key players in neural circuitry formation for the establishment of proper neuronal connectivity, relying on the precise interaction of combinatorial sets of molecules (Hassan and Hiesinger, 2015). A potential molecular candidate is neuromusculin, nmr, a homophylic cell adhesion molecule which plays a role in clustering cells of the peripheral nervous system, neuronal fasciculation, and pathfinding. Nonetheless, its importance in synaptic targeting is not well understood. Thus, our goal is to determine the role of neuromusculin in the formation of Drosophila's hardwired mechanosensory system.

Methods: 455-GAL4 driver was used to selectively express UAS-dsRNA in the scutellum to ensure that RNA interference did not perturb the postsynaptic neural circuitry. Two-day old females were sorted according to their genotype into three groups: 455-GAL4/+ (control group), in 455-GAL4 / UAS-dsRNA nmr (dsRNA nmr), and 455-GAL4 / UAS-TRiP siRNA nmr (TRiP nmr). For the behavioral assay, after decapitation, the flies from dsRNA nmr (n = 30) and the control group (n = 51) were placed in a humidified chamber to recover for one hour, followed by a test for responsiveness of the anterior notopleural (aNp) and posterior scutellar (pSc) neurons cleaning reflex. The presence or absence of response was scored visually, and considered a positive response as the successful movement of the rear pair of legs towards the labelled bristles. Additionally, carbocyanine dye labeling was performed in fixed flies of each group (n = 20) to assess the morphology of pSc mechanosensory axons (Kays et al., 2014).

Results: In order to assess association between the control and neuromusculin groups, a chi-squared test for independence was performed. Nmr had a significantly different cleaning reflex frequency response when compared to control ($p < 0.01$). In terms of morphology, when compared to the control group neuromusculin experimental groups (dsRNA nmr, and nmr) consistently presented a strong phenotype, composed of five axonal targeting errors as well as pronounced changes to their axonal harbors, especially primary branches. The phenotype is reliable in terms of morphology and penetrance (67% for dsRNA nmr, and 50% for TRiP nmr).

Conclusion: As demonstrated by our results, neuromusculin is involved in the development of the hardwired mechanosensory circuit of the pSc neuron. Further insight might require molecular biology and biochemical experimental assays.

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B32) MRI Evidence of Acute Inflammation in Cortical Gray Matter of Early Multiple Sclerosis Patients

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Objective: To identify gadolinium enhancing lesions affecting the cortex of early MS patients and to describe the frequency and evolution of these lesions.

Methods: We performed a retrospective observational longitudinal analysis of MRI scans collected for the BECOME study (Betaseron vs Copaxone in Multiple Sclerosis with Triple-Dose Gadolinium and 3- Tesla MRI Endpoints). 75 early stage MS patients were scanned monthly, over a period of 12 to 24 months, using 3T MRI after administration of triple-dose gadolinium. 1188 scans were included in the analysis. 139 were selected using an image pipeline algorithm that integrated the image information of cortical grey matter (GM) masks and gadolinium-enhancing lesions masks. These scans were evaluated to identify gadolinium-enhancing lesions affecting the cortex

Results: The total number of gadolinium-enhancing lesions was 2044. The number of gadolinium enhancing lesions affecting the cortex was 120 (6%). The number of patients that showed gadolinium enhancing lesions affecting the cortex was 27 (36%). The number of gadolinium-enhancing lesions affecting the cortex at baseline was 25 (21%) and the number of new lesions that developed in follow up scans was 49 (41%). The number of persistent lesions was 46 (38%).

Conclusion: The presence of enhancing lesions affecting the cortex and adjacent white matter, although transient and not frequent, suggest that at least some cortical lesions are related to bloodbrain-barrier (BBB) leakage. Our study serves as a preliminary, proof-of-concept that there may be an acute inflammatory phase in the development of some MS cortical lesions, which can be tracked with gadolinium-enhanced MRI.

B33) Developmental song exposure shapes behavioral and neural song responses in adult zebra finches: Can social experience rescue species-typical behavior in song-naive birds?

Erin Wall, Therese Koch, Dr. Sarah Woolley

Vocal communication is a critical component of social behavior. However, in order for receivers to properly respond to vocal signals, they must detect and respond to ethologically relevant information in vocal signals. Songbirds provide an ideal model for studying the neural basis of perception of natural communication signals. In songbirds, males produce learned vocal signals ('songs') which contain information about the identity, quality, and motivation of the singer. Females do not sing but use songs to identify individuals and select mates. For example, male zebra finches perform a longer, faster, more stereotyped version of their song when singing to females, and females prefer this high-performance courtship song even when the singer and his song are unfamiliar. Interestingly, the preference for high-performance song is not innate but is dependent on developmental auditory experience. In particular, females raised without exposure to song ('song-naïve' birds) do not show consistent preferences for high-performance courtship song. However, whether there is a critical period during which females must hear song in order to express species-typical song preferences and auditory encoding remains unclear. Here, we manipulated the auditory experience of song-naïve females during adulthood to determine whether adult experience can 'rescue' the neural and behavioral phenotypes. In a series of experiments, we found that song-naïve females and normally-reared females differ in their preferences for songs from individual males. Exposure to song through an active choice task did not normalize the song preferences of song-naïve females. In addition, passive song exposure during adulthood also did not normalize markers of neural plasticity in secondary auditory areas of song-naïve females. Thus, adult auditory experience does not appear sufficient to normalize responses of birds raised without song exposure. Current studies are investigating whether social interactions, such as mating, may be more effective at shaping the neural and behavioral responses of song-naïve females in adulthood.

B34) Myelinated Nanofibers - A Nanoengineered Oligodendrocyte Culture System

Daryan Chitsaz, Timothy E. Kennedy

The capacity to study myelination *in vivo* has been dramatically enhanced by advances in genetics and imaging; however, complementary high-throughput *in vitro* systems are relatively limited. Recent publications (Lee *et al*., 2012; Bechler *et al*., 2015) have provided an option with great potential, demonstrating that oligodendrocytes are intrinsically capable of forming layered myelin basic protein-containing ensheathments around engineered nanofibers that mimic axons in culture. Created via electrospinning, these nanofibers can be made with custom sizes, mechanical properties, coatings, and even microcontact-printed patterns, facilitating the study of how oligodendrocytes respond to biomechanical and chemical cues from axons. These cultures are also highly amenable to live imaging and automated image analysis. We have adopted this method in the interest of characterizing how oligodendrocytes interact with axons in a controllable environment, and exploring its usefulness as a system to screen for effects of pharmacological or genetic manipulations on myelin development and maintenance. We aim to extend the utility of this system as a model of physiologically-relevant myelination, with the scalability of traditional 2D cell culture.

B35) Single population of primary afferents are capable of coding distinct behaviors: Itch and Pain distinction by MrgprA3 expressing C-Fibers

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Itch, or pruritus, can be described as an unpleasant sensation that leads to scratching behavior or the desire to scratch. Due to high prevalence in numerous diseases and widespread occurrence as a side effect of many medications, itch has become a prevailing research topic in recent years. Despite significant structural and behavioral overlap of pruriception and nociception, the underlying neurophysiological basis of itch sensation and its relation to pain is still unclear. More specifically, the enigma of how the somatosensory system differentiates itch and pain sensations and triggers distinct fight or flight behaviors remains to be solved.

To investigate such distinction, we designed studies on animals with selective expression of excitatory DREADD (hM3Dq) and/or Channelrhodopsin2 (ChR2) in MrgprA3 neurons. These primary nociceptors constitute a subpopulation of C-fibers known to be specifically linked to itch (Han et al., 2013). Functionality of the actuators is validated *in vitro* using calcium imaging and electrophysiology. As expected, behavioral studies show that chemogenetic activation of these neurons evokes stereotypical itch behavior rather than pain responses. Surprisingly, optical activation of these neurons through ChR2 predominantly induces pain avoidance behaviors rather than scratching.

Our results show that *in vivo* a single population of C-fibers can convey itch sensation in certain conditions and pain in others. This calls for novel models to explain how itch and pain are distinctly coded in the central nervous system.

B36) The Shh receptor Boc induces DNA damage in cerebellar granule cell precursors.

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Introduction: Cerebellar granule cell precursors (GCPs) proliferate in response to Sonic hedgehog (Shh). Prolonged activation of the canonical Shh pathway during development can lead to the formation of medulloblastoma (MB), the most common brain malignancy in children. Our lab has established a model in which active Shh signaling in Ptch1 heterozygous mice induces high levels of proliferation leading to DNA damage. This drives Ptch1 loss-of-heterozygosity, which causes constitutively active Shh signaling and tumorigenesis. Although we have also shown that the Shh receptor Boc is upregulated in both human MB and mouse models of MB, the role that this high expression of Boc plays in tumor formation is unknown.

Objectives: 1- To test if Boc upregulation is sufficient to induce DNA damage, 2- To identify the downstream mediators of Boc-induced DNA damage, and 3- To demonstrate that Boc overexpression (OE) triggers DNA damage *in vivo*.

Results and Conclusions: Using dissociated GCPs from postnatal mice that were electroporated with a Boc-GFP plasmid or a GFP control plasmid, we showed that Boc can induce DNA damage, as measured by the fluorescence intensity of γH2AX (phosphorylated H2AX, a marker of DNA damage). This effect does not require the Boc cytoplasmic tail. Through a screen of small molecule inhibitors, we determined that this DNA damage is not mediated by the pathways already known to be downstream of Boc activity, indicating that it is likely mediated through a novel signaling mechanism. Through *in vivo* electroporation of the cerebellum in postnatal day 1 mice, we demonstrated that Boc OE leads to an increase of GCPs with DNA damage *in vivo*.

Based on these results, we conclude that Boc upregulation, both *in vitro* and *in vivo*, is sufficient to induce high levels of DNA damage. We are currently determining the signaling cascade mediating this effect. Our next step will be to test if high levels of Boc expression can accelerate MB tumorigenesis *in vivo*.

B37) mGluR5 in amphetamine sensitization: a [^{11}C]ABP688 PET study in healthy volunteers

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Background: The metabotropic glutamate receptor subtype 5 (mGluR5) modulates neurotransmission and regulates some forms of synaptic plasticity. In animal models, inhibiting this receptor affects behavioural and drug-seeking responses to psychostimulant drugs such as cocaine and amphetamine. In studies in humans, reduced availability of this receptor has been observed in patients with cocaine use disorders, as measured by positron emission tomography (PET) and the selective mGluR5 ligand, [^{11}C]ABP688. It is not yet known if this reflects a pre-existing vulnerability or an adaptation to repeated drug use. The objective of this study was to use PET with [^{11}C]ABP688 to assess the relationship between striatal mGluR5 levels and psychomotor responses to a repeated d-amphetamine regimen that produces sensitization in healthy volunteers.

Methods: Eighteen healthy, stimulant-naïve volunteers (13 female, 5 male) were randomly assigned to receive four oral doses of 0.3mg/kg d-amphetamine (Dexedrine) or placebo. Treatment was administered in three consecutive sessions approximately 48 hours apart, followed by a challenge dose 16 days later. Behavioral responses to the drug were assessed by measuring rate of speech and subjective ratings of activation and alertness on visual analog scales (VAS, 0-10). Behavioral *sensitization* was defined as a significantly larger response to the fourth amphetamine dose as compared to the first.

All participants underwent two one-hour high-resolution HRRT PET scans with 370mBq [^{11}C]ABP688, once prior to the first amphetamine dose and a second immediately prior to the final challenge dose. Regional binding potential (BP_{ND}) values were calculated relative to a cerebellar grey matter reference region for associative, sensorimotor, and ventral subregions of the striatum.

Results: Behavioral sensitization was observed in the drug group (n=10) on measures of speech rate and subjective ratings of racing thoughts (VAS - “Mind Racing”) (mean change in number of words spoken per 5 minutes at challenge vs. dose 1: +49.1 SD 38.7, p=0.003; mean change in VAS - Mind Racing score +2.7 SD 3.4, p=0.035).

[^{11}C]ABP688 BP_{ND} values were significantly higher in men relative to women (p=0.037). Controlling for this sex difference, BP_{ND} did not differ between drug and placebo groups at baseline or follow-up. In the drug group, BP_{ND} at follow-up was negatively correlated with subjective ratings of racing thoughts following the challenge dose in all three striatal subregions (associative r=-0.84, p=0.003, sensorimotor r=-0.81 p=0.004, ventral r=-0.75 p=0.013). In female participants, a trend was observed towards a negative correlation between BP_{ND} in the sensorimotor striatum and increase in speech rate at challenge dose (r=-0.75, p=0.054).

Conclusion: These results suggest that lower mGluR5 availability in the striatum following

a repeated amphetamine administration regimen is associated with more pronounced psychomotor responses to a subsequent d-amphetamine challenge in healthy volunteers. Given that such responses are linked to increased drug-seeking behaviors in animal models, these results are consistent with the hypothesis that low striatal mGluR5 may be an early indicator of risk for developing stimulant dependence, as well as being a potential target for treatment.

B38) Environmental stressors modify developmental neurobiology and adult foraging and mating behaviours of *Caenorhabditis elegans*

Connie Li*, Sreeparna Pradhan, Michael Hendricks

In an overcrowded environment marked by food scarcity, the nematode *Caenorhabditis elegans* undergoes dauer arrest. If bacterial concentrations are replenished, development resumes, affecting signaling pathways in neurons and giving rise to behavioural changes. This project investigates the effect of starvation on the foraging and mating behaviours of *C. elegans.* Within a microfluidic environment, temporal pulses of bacterial solutions modify the trajectories of well-fed and post-dauer young adult animals. By recording the trajectories and resolving them as vectors, we demonstrate that post-dauer animals exhibit a greater tendency for sharp turns. These spiral-like movements are characteristic of local search, a locomotion strategy that permits worms to dwell closer to areas of food. Meanwhile, by outcrossing different hermaphrodites with wild-type Hawaiian males, we show that post-dauer hermaphrodites have a higher mating frequency. Hence, this suggests that starvation does not only alter food-seeking, but also reproduction. As the divergence between well-fed and post-dauer worms has been evidenced at the molecular level, this project aims to identify the behavioural differences subsequent to early life stress.

B39) The Role of Actin Nucleator Spire in the Development and Maintenance of Dendritic Arbors

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Developing dendrites form complex arbors that influence the strength and specificity of their connections with presynaptic axons. Research to uncover novel cellular and molecular mechanisms that control the morphogenesis and maintenance of dendrites is important, since progress in this area will provide insight into how neural circuits are constructed. This could, in turn, contribute to therapeutic stratagies for neurodegenerative/developmental disorders, and for repair of neural circuits after brain injury.

Filaments of actin (F-actin) are remodelled within the dendritic cytoskeleton through regulated nucleation, elongation and disassembly. Spire is an actin nucleation factor known to co-operate with Formins for F-actin assembly. Our lab showed previously that Spire is required for the proper density and positioning of branches within dendritic trees of Drosophila sensory neurons. Loss of Spire also affects circuit function, as demonstrated by the loss of “nocifensive” escape responses in Spire deficient larvae.
The molecular mechanisms underpinning Spire’s effect on dendrite growth remain poorly understood. With some sequence homology to Rabphilin 3A, Spire could interact with members of the Rab family of small GTPases. This raises the possibility that Spire links F-actin assembly with Rab-regulated protein and vesicle trafficking through the endosomal/secretory pathway. However, the importance of a Spire and Rab interaction in neurons, *in vivo*, remains completely unknown.

Using live *in vivo* imaging we have found that Spire is distributed in a punctate pattern in Drosophila dendritic arborisation neurons. We are now determining whether Spire and Rabs co-localise in dendrites, and the influence of this relationship on arborisation. Since trafficking via the endosomal/secretory pathway is a dynamic process we are also tracking fluorescently labelled Spire and Rab using time-lapse microscopy. We are using anti-GFP immunoprecipitation to pull-down YFP tagged Rabs from lysates of nervous system tissues, and performing anti-Spire Western blots to establish whether these proteins interact *in vivo*.

The results of this research will contribute to our understanding of Spire function in dendrites, and further our understanding of the development and remodelling of dendritic trees.

B40) Depression as a Gut Feeling: The role of the gut in the link between early life stress, chronic inflammation, and adult depression.

Sarah Barnett Burns, Kasia Szyszkowicz, Florence Brun, Gustavo Turecki, Giamal Luheshi.

Depression is one of the leading causes of global disability, with high rates of treatment resistance and recurrence. Multiple lines of evidence suggest that early life stress (ELS) causes a vulnerability to subsequent stressors via neuroimmune dysregulation and an increased risk for depression later in life. Recent animal studies suggest that the gut-brain axis is a powerful modulator of both the stress response and the immune system, however, a direct link between gut dysbiosis and depression has yet to be fully investigated. Using two established ELS mouse models, limited bedding, and maternal separation, we found sex specific effects of ELS on corticosterone reactivity, circulating cytokines, behaviour, gut dysbiosis, and hippocampal neuronal area. Although we did not find any alterations in microglia in the hippocampus, the severity of gut dysbiosis significantly predicted the decrease in hippocampal neuronal area. In addition, we found similar patterns of gut dysbiosis in postmortem human intestines from depressed suicides as compared to sudden death controls. These preliminary data suggest that the gut immune system may be altered in ELS and depression.

Instructions for Presenters

You must stand by your poster during your assigned poster session.

Putting up your posters
Session A and B posters must be put up between 8:30AM and 12:00PM on Thursday September 21st.
All posters must be removed between 3:00PM and 3:15PM on Friday September 22nd.
Please plan on leaving your poster up both days, regardless of which session you are signed up for.

N.B. If you submitted an abstract, but fail to present a poster, you will be fined for the cost of the poster board.