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ABSTRACT BOOKLET

SESSION 'A'

September 20 2018: 12:50 – 14:30

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Cerebellar stellate cell excitability is regulated by coordinated shifts in voltage-gated Na⁺ and K⁺ channels

A-01

Ryan P.D. Alexander*, John Mitry, Vasu Sareen, Anmar Khadra, Derek Bowie

Although it is generally assumed that basic neurophysiological properties measured in vitro using whole-cell patch-clamp electrophysiology are comparable to their behaviour in vivo, there have been few attempts to characterize changes induced during patch-clamp investigation. Using whole-cell patch clamp in acute cerebellar slices, we observed drastic increases in excitability in both cerebellar stellate cells and granule cells, but not in Purkinje cells, over a 25-minute recording duration. In stellate cells, this phenomenon was accompanied by a decrease in spike latency and hyperpolarization of action potential (AP) threshold. Using an augmented Hodgkin-Huxley firing model, we predicted modulation of both voltage-gated sodium channel (Nav) and potassium channel (Kv) gating properties, with a primary role for the shift of Nav. Measuring these isolated responses in whole-cell voltage-clamp configuration confirmed that Nav voltage-dependence of activation as well as channel availability shift substantially over the course of the experiment, whereas delayed rectifier Kv gating remained stable. Surprisingly, large shifts were also observed in A-type Kv properties that affect AP frequency but not threshold. These findings demonstrate the challenges associated with this experimental technique, and the susceptibility of certain cell types for dramatic changes in basal functional properties. Furthermore, they also suggest new modes of long-term plasticity of excitability mediated through modulation of Nav channels.

How much do EEG studies inform the education practice about reading disabilities

A-02

Badriah Basma*, Armando Bertone

Literature examining reading disabilities and brain activity is growing, with most research using electro-encephalography (EEG) as a method to examine a different aspect of the reading processes in the brain. The purpose of this systematic review is to address the following question; 'How do EEG studies help us understand reading disabilities in young children?' We first conducted a tertiary systematic review, examining all available systematic reviews on EEGs and reading disability. This resulted in no quality reviews. We then sought to answer this question by locating relevant studies by exploration of the grey literature. We used electronic databases to search for studies using EEG that explored reading disabilities, which included PubMed, Web of Science, and PsycINFO. To perform this systematic review, we used the following keywords; 'reading disability' OR 'Dyslexia' OR 'reading difficulty' AND 'EEG' OR 'Electroencephalography.' The search was completed with a time (2008-2018) and age (4 - 9 yrs. old) restriction. Basic inclusion/ exclusion criteria driven from available literature was used and included studies that (i) only had participants with a reading disability/difficulty, (ii) the reading disability was not a result of a head trauma or brain injury, (iii) a reading-relevant event-related potential (ERP) (i.e., N400) was measured, and (iv) was based on a reading instruction task. Using these criteria, this systematic review resulted in 12 studies. A common finding among the 12 studies was that young children with reading disabilities have greater left lateralization which points to an underperformance in the left hemisphere when decoding words.

Synaptopodin is necessary for homeostatic upscaling

Jennifer Boateng*, Melanie Chan, Philip Chang, Anne McKinney

A-03

The remarkable ability of neurons to alter the strength of their synaptic connections is considered the mechanistic foundation for learning and memory, but these same mechanisms can also destabilize normal neural network function when uncontrolled. Homeostatic scaling is a negative-feedback process that maintains neuronal activity within optimal ranges. Homeostatic scaling involves the trafficking of a subtype of glutamate receptors, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors at excitatory synapses. The relevant cellular machinery involved in AMPA receptor trafficking are often found within dendritic spines, the primary sites for excitatory postsynaptic contacts. A subset of larger dendritic spines possesses the actin-binding protein synaptopodin. While synaptopodin has been documented to promote Hebbian plasticity, spatial learning and is involved in AMPA receptor trafficking, its function within the context of homeostatic synaptic scaling remains unknown. Whether synaptopodin converges with other synaptic scaling elements such as tumor necrosis factor alpha (TNF α), an inflammatory cytokine that has direct influence on AMPA receptor upregulation and is implicated in homeostatic upscaling, is unknown. Here, we set out to investigate the role of synaptopodin in homeostatic scaling. Wildtype (WT) and synaptopodin knockout (SPKO) organotypic hippocampal cultures were treated with tetrodotoxin, a sodium channel blocker for 3-4 days, to induce chronic inactivity or picrotoxin, a GABAA receptor antagonist for 2 days, to stimulate hyperexcitability. Whole cell electrophysiology was used to measure AMPA mediated miniature excitatory postsynaptic currents (mESPC) in WT and SPKO CA1 pyramidal neurons. Wildtype CA1 pyramidal neurons were able to scale up the amplitude of AMPA mediated currents during chronic inactivity but CA1 pyramidal neurons lacking synaptopodin were unable to undergo upscaling during prolonged inactivity. While the release of TNF α was observed in WT pyramidal neurons, SPKO neurons did not release TNF α during prolonged inactivity. Since TNF α is required for inactivity induced synaptic scaling, exogenous TNF α was added to both WT and SPKO cultures. The addition of exogenous TNF α was not able to restore scaling in SPKO neurons suggesting either insensitivity to TNF α receptor or improper TNF α signaling. Expression levels of tumour necrosis factor receptor 1 (TNFR1), the predominant TNF α receptor in the central nervous system, were equivalent in both WT and SPKO neurons. The equivalent expression levels of TNFR1 in WT and SPKO lead us to hypothesize that there is improper TNF α signaling in SPKO neurons. Western blots of p-Akt and NF κ B, downstream effectors of TNF α , are being conducted to determine whether there is proper TNF α signaling in SPKO neurons. The findings from this study show that synaptopodin is necessary for homeostatic upscaling and its absence results in the inability to scale during prolonged inactivity. These results contribute to the evolving literature on synaptic scaling and enhance our knowledge of the potential mechanisms involved.

Quantitative sensory testing as a clinical pain assessment tool in children and adolescents suffering from chronic pain

A-04

Alice Bruneau*, Pablo M. Ingelmo, Catherine E. Ferland

AIMS: The application of semi-quantitative tools may help clinicians to improve treatment protocols. Quantitative sensory testing (QST) provides information on the mechanisms of pain transduction, modulation and perception using cutaneous mechanical and thermal procedures. The aim of the present research was to evaluate the potential applications of QST in a pediatric chronic pain clinic. **METHODS:** Before receiving treatment, patients were assessed with QST for the presence of pain peripheral and central sensitization as well as for the efficacy of their endogenous inhibitory pain control evaluated with a conditioned pain modulation (CPM) paradigm. The medical charts and QST values were reviewed and analyzed retrospectively. The primary end-point was the proportion of patients receiving pain medication based on the conditioned pain modulation (CPM) results. **RESULTS:** The 116 patients assessed had a mean age of 14.9 ± 2.0 years old, of which 99 were girls. Among the patients, 67% presented with peripheral sensitization, 40% had central sensitization and 53% demonstrated suboptimal CPM. Of the patients with a suboptimal CPM, 26.4% received antidepressants, compared to 8.7% for patients with an efficient CPM ($\chi^2 = 5.198$, $p=0.023$). **CONCLUSION:** QST evaluations provided the treating team with valuable information regarding the presence of peripheral sensitization, central sensitization and the efficiency of the endogenous descending pain inhibitory pathway. These results suggest that QST can be used to guide treatment in the daily clinical practice. Further investigations are needed to evaluate if CPM is associated with clinical improvement of the patients.

Norepinephrine enhances vocal learning by promoting the sensory encoding of communicative signals

A-05

Yining Chen*, Jon T. Sakata

Learning the acoustic structure of communicative sounds forms the basis of vocal learning. Indeed, it is important to memorize the sound of a signal before learning the motor commands to produce the sound. As such, it is critical to understand the processes underlying auditory learning to reveal mechanisms of vocal learning. Catecholamines such as norepinephrine (NE) have been implicated in auditory learning for vocal learning. We investigated the extent to which NE modulated the auditory learning of communicative signals ('songs') in the zebra finch, a songbird that learns its song in a manner that parallels how humans acquire speech. We have previously demonstrated that NE-synthesizing neurons are more active under conditions that promote the sensory learning of song. To determine whether NE can enhance auditory learning for vocal learning, we infused NE into an auditory processing area implicated in sensory learning as juvenile songbirds heard song for the first time in their lives. Relative to control birds, birds that were given NE during song tutoring produced songs as adults that were significantly more similar to the songs they were tutored with. Furthermore, birds given NE during tutoring (but not control birds) showed evidence of song learning within days of tutoring. These findings indicate that NE significantly and rapidly promotes the sensory learning of song in the service of vocal learning and suggests the possibility that NE in auditory processing areas could contribute to speech learning in humans.

Channelrhodopsin-2-induced synaptic plasticity in neocortical interneurons

Christina You Chien Chou*, Wendy Yan, P. Jesper Sjöström

A-06

Spike timing-dependent plasticity (STDP) has been studied extensively at connections between excitatory neurons, which are key carriers of information in neocortex. However, inhibitory neurons, through feedback and feedforward inhibition, are indispensable to proper circuit function. There is increasing evidence showing that plasticity is determined by synapse type, in a manner that matches the functional specificity of different interneuron types. However, experimenters aiming to study STDP must currently carry out slow and experimentally challenging whole-cell recordings from connected pairs of neurons. To address this problem, we combined cell-type specific expression of Channelrhodopsin-2, laser photostimulation, and slice electrophysiology to develop a high throughput method for studying plasticity. Here, we present preliminary results showing optogenetically induced long-term plasticity at pyramidal cell afferents onto basket cells and Martinotti cells in layer 5 of the developing mouse visual cortex.

Effects of glial heme oxygenase-1 on neuronal -synuclein in the GFAP.HMOX1 mouse model of Parkinson's Disease

A-07

Marisa Cressatti*, Wei Song, Ariana Turk, Carmela Galindez, Hyman M. Schipper

OBJECTIVE: To determine whether astroglial HO-1 transduces environmental and endogenous stressors into patterns of neural damage which promote the toxicity of neuronal -synuclein.

BACKGROUND: The product of the stressor-inducible HMOX1 gene, heme oxygenase-1 (HO-1) is highly overexpressed in astrocytes of the substantia nigra in patients with idiopathic Parkinson's disease (PD). There is considerable evidence implicating HO-1 in the pathogenesis of PD, and overexpression of astroglial HMOX1 in vitro to levels seen in post-mortem PD brain promotes pathological iron deposition, oxidative stress, mitochondrial damage and macroautophagy characteristic of the human disorder. We recently engineered conditional GFAP.HMOX1 transgenic mice that selectively overexpress human HO-1 in astrocytes. Transgene expression in these mice between 8.5 and 19 months of age results in a parkinsonian phenotype characterized by oxidative stress; basal ganglia siderosis; mitochondrial damage; nigrostriatal hypodopaminergia associated with locomotor incoordination and stereotypy; and overproduction of -synuclein mRNA and protein. -Synuclein is a key player in PD pathogenesis and a major constituent of hallmark Lewy pathology. While precise mechanisms of abnormal -synuclein aggregation remain disputed, there is fair consensus implicating oxidative reactions in this process. **RESULTS:** Primary WT neurons co-cultured with GFAP.HMOX1 astrocytes exhibit enhanced protein oxidation, mitophagy, and apoptosis, aberrant expression of genes regulating the dopaminergic phenotype and imbalance in genes regulating mitochondrial biogenesis. The latter abnormalities were abrogated by siRNA knock-down of -synuclein, implicating -synuclein as a key mediator of HO-1's neurodystrophic effects. We also identified two microRNAs (miRNA) that negatively regulate -synuclein in GFAP.HMOX1 mouse brain and periphery, namely miR-153 and miR-223.

CONCLUSIONS: Taken together, HO-1 downregulates miR-153 and miR-223 which in turn upregulates -synuclein in the GFAP.HMOX1 mouse brain. These results highlight the importance of -synuclein as a therapeutic target, potentially via miR-153 or miR-223, in the treatment of PD.

The interaction between circadian dysfunction and a neurodevelopmental risk factor for Schizophrenia

A-08

Tara Delorme*, Nicola M. Ludin, Lalit Srivastava, Nicolas Cermakian

One of the many challenges in developing effective treatments for those suffering from psychiatric disorders, including schizophrenia, is that these disorders are multifaceted in nature. They are likely triggered through a complex set of interactions between genes, environmental exposures, and neurodevelopmental processes. These interactions are currently poorly understood. We hypothesize that circadian disturbance, an environmental exposure, contributes to the development of schizophrenia. We are using a well-established neurodevelopmental mouse model of schizophrenia based on maternal immune activation (mIA). On gestational day 9.5, pregnant dams receive a single injection of the viral mimic polyinosinic:polycytidylic acid (polyIC) or vehicle. The resulting polyIC-exposed offspring display schizophrenia-like phenotypes. We first investigated if circadian clock abnormalities are associated with this mIA model. Mice were placed in running wheels and exposed to different lighting environments: 12h light: 12h dark cycles (LD12:12), a 6-hour phase advance, constant darkness (DD) and constant light (LL). In LD12:12, polyIC exposed offspring were more active in the light phase than controls ($p=.006$), as well had significantly higher interdaily stability ($p=.011$) and a significantly shorter alpha than controls ($p=.0052$). After a 6-hour phase advance, both groups re-entrained similarly to the new light-dark cycle. Results from the DD and LL light conditions are being analyzed. We also investigated if disrupting the circadian clock with LL interacts with mIA and exacerbates schizophrenia-like behaviours. Our results indicate an interaction between circadian disruption and treatment group on anxiety-like behaviour. Results from prepulse inhibition of acoustic startle and Crawley's social interaction test are being analyzed. The preliminary data show that the circadian clock is likely impaired in the polyIC-exposed mice, and that the circadian clock interacts with mIA to exacerbate schizophrenia-like behaviour. Rescuing these circadian abnormalities may provide new therapeutic strategies to control or prevent schizophrenia and related psychosis.

Aging mice show motor deterioration and Purkinje cell firing alterations

A-09

Eviatar Fields*, Sriram Jayabal, Alanna Watt

Canada is facing a growing 'aging epidemic' arising from the economic burden of an aging population. Declines in motor coordination, impaired gait, and balance deficits are common changes that accompany aging and limit a person's quality of life and independence. The cerebellum is critically involved in motor coordination and motor learning. Cerebellar Purkinje cells fire spontaneous action potentials at high frequencies, which is disrupted in mouse models of ataxia. Therapeutic interventions that rescue Purkinje cell firing rate deficits have been shown to improve motor coordination in ataxic models, suggesting that high frequency firing is important for normal cerebellar function. It has been hypothesized that neurodegenerative diseases like ataxia share common mechanisms with aging, yet little is known about Purkinje cell firing properties in aged animals to date. We wondered whether healthy aging mice might share similar cerebellar alterations as ataxic mice. To address this, we studied motor coordination and gait in healthy C57Bl/6J mice at several ages from young to old adult. We then performed loose cell-attached recordings of Purkinje cell action potentials in acute cerebellar slices at these time points. We found that motor coordination declined with age, and that this was accompanied by an age-dependent reduction in Purkinje cell firing rates that was reminiscent of the changes observed in ataxia models. These findings suggest that cerebellar-related motor decline observed in healthy aging and in ataxia may share similar mechanistic underpinnings.

Topical combination of Meldonium and N-Acetyl Cysteine for the treatment of CRPS-1 and neuropathic pain

A-10

Oli Abate Fulas*, André Laferrière, Terence J. Coderre

AIM OF INVESTIGATION: Neuropathic pain and complex regional pain syndrome type-1 (CRPS-1) are among the common manifestations of chronic pain. Currently available analgesics for CRPS-1 and neuropathic pain have poor efficacy and come with a multitude of dose limiting systemic side effects. One approach to tackle this problem is incorporating drugs that target peripheral mechanisms into topical formulations to allow local delivery of therapeutic dose levels all the while avoiding the occurrence of systemic side effects. This study investigates the analgesic use of the topical combination of drugs meldonium and N-acetyl cysteine (NAC). Meldonium is an inhibitor of fatty acid β -oxidation and stimulator of glucose uptake and utilisation. It is also hypothesized to activate endothelial nitric oxide synthase (NOS). NAC is an endogenously existing amino acid derivative that is also reported to increase endothelial NOS expression in vascular tissue. We tested the anti-allodynic effect of the topical combination of meldonium and NAC in rat models of CRPS-1 and neuropathic pain. To test the involvement of NOS in the anti-allodynic effects seen with this topical combination, we also investigated the influence of pretreatment with a non-specific NOS inhibitor on the topical analgesic effect of the combination. **METHODS:** Topical formulation of an equimolar combination of meldonium and NAC, using a polyethylene-glycol-base-system, was prepared and applied to the hind paws of chronic post-ischemia pain (CPIP) and chronic constriction injury (CCI) rat models of CRPS-1 and neuropathic pain, respectively. CPIP rats were generated using 3-hour-long hind paw ischemia and reperfusion where as CCI rats were made by applying loose chromic-gut ligatures to the sciatic nerve. The level of mechanical hypersensitivity was measured by an up-down paw withdrawal threshold (PWT) procedure using von Frey hairs. To investigate the involvement of NOS in the anti-allodynic effect of the combination, the rats were pretreated with intraperitoneal injection of L-Nitroarginine methyl ester (L-NAME) 30 minutes prior to topical application and subsequent PWT measurement. **RESULTS:** The acute topical application of the meldonium-NAC combination significantly relieved mechanical allodynia in both the CPIP and CCI rat models of CRPS-1 and neuropathic pain. Moreover, repeated daily administration of the combination resulted in longer lasting anti-allodynia and gradually improved the rats' pretreatment baseline PWT on successive days. The acute anti-allodynic effect seen in CPIP rats following topical administration of the meldonium-NAC combination was reversed after systemic pretreatment with L-NAME. **CONCLUSIONS:** In the rat CPIP and CCI models of CRPS-1 and neuropathic pain, the topical combination of meldonium and NAC produces significant relief from mechanical allodynia. The duration of ant-allodynic effect increases with repeated daily topical application. The acute anti-allodynic effect of the topical combination of meldonium and NAC is reduced by NOS inhibition implying that the drug works via peripheral mechanisms that involve NOS modulation.

Sex differences in the contributions of spinal atypical PKCs to the maintenance of centrally-mediated persistent pain

A-11

Nicole C. George*, André Laferrière, Terence J. Coderre

BACKGROUND: The atypical PKC isoform PKM zeta (PKM ζ) has been implicated in the maintenance of hippocampal plasticity and memory, as well as the spinal nociceptive sensitization underlying persistent pain hypersensitivity. While the isoform PKC iota/lambda (PKC ι/λ) has been established in hippocampal plasticity, there has been little investigation into its role in nociception, though PKM ζ -dependent sex difference suggest that PKC ι/λ may contribute to female-specific mechanisms. Thus, the purpose of this study was to clarify the roles of spinal atypical PKC isoforms and their downstream targets in the maintenance of persistent pain across the sexes. **METHODS:** Cell-permeable inhibitors to PKM ζ , PKC ι/λ and downstream targets (p62/GluA1 and NSF/GluA2, respectively), or corresponding control peptides, were delivered intrathecally (i.t.) to Long Evans hooded rats. Nociceptive behaviours induced by intraplantar (i.pl.) injection of formalin (2%), repeated intramuscular (i.m.) injections of acidic saline, and i.t. calcitonin gene-related peptide (CGRP) were assessed through paw withdrawal thresholds (PWTs) and sustained nociceptive behaviours (SNBs). **RESULTS:** Acidic saline-induced allodynia was reversed in male animals following broad inhibition of both isoforms, as well as PKC ι/λ and p62/GluA1. The inhibitors were not effective in females, or for either sex in the formalin test. NSF/GluA2 disruption reversed allodynia for both males and females in the acidic saline test but did not have an effect for either sex in the formalin test or following i.t. CGRP. **CONCLUSIONS:** These findings demonstrate a male-specific role for both atypical PKC isoforms, limited to pain states which depend mainly on central sensitization. While the sexual divergence appears to converge at the NSF/GluA2 interaction, these findings suggest that females rely on a factor independent of atypical PKCs for the maintenance of centrally-mediated persistent pain.

Knock-in zebrafish model expressing the analogous ALS-causing TDP-43 variant [A382T] shows early motor deficits and reduced expression of *tardbp*

A-12

Ziyaan Harji*, Gary A.B. Armstrong

Mutations in TARDBP, encoding TAR-DNA Binding Protein of 43 kDa (TDP-43), are associated with amyotrophic lateral sclerosis (ALS). Until recently, modelling ALS in animals has relied upon transgenic overexpression of either human mutant or wild type TARDBP. With the advent of the CRISPR/Cas9 system, researchers now have the opportunity to generate analogous knockin mutations in endogenous genes of model system orthologs. Using this method, we have created a zebrafish model of ALS that carries the equivalent A382T (zebrafish A379T) variant. The A382T variant shows complete penetrance by the age of 80 and is recognized as the most commonly found disease-associated TDP-43 variant. We believe that this mutant zebrafish line will allow us to more accurately recapitulate the genetic aetiology of familial ALS and permit us to examine both cellular and physiological defects that arise in this neurodegenerative disease. In preliminary experiments, we have observed that mutant fish exhibit reduced survival and display a motor phenotype at larval stages of development. In addition, fish that are homozygous for the mutant allele show reduced expression of *tardbp*. In addition to *tardbp*, the zebrafish genome contains a paralog, *tardbpl*, from which a unique splice variant (*tardbpl* V1) can compensate for the loss of zebrafish *tardbp* expression. To mitigate any potential compensatory effects of *tardbp* V1, we will also examine defects that arise in zebrafish that carry the A379T variant in the *tardbpl*^{-/-} genetic background. We predict that zebrafish with the A379T variant in the *tardbpl*^{-/-} background will develop a more severe motor phenotype.

High salt intake causes cytoskeleton reorganization in vasopressin neurons of the supraoptic nucleus

Suleima Jacob-Tomas*, Masha Prager-Khoutorsky

A-13

High dietary salt (HDS) strongly correlates with cardiovascular diseases and is a major factor contributing to the pathogenesis of hypertension. Recent studies show that HDS leads to neurogenically-mediated increases in sympathetic activity, vascular resistance, and water and sodium retention, revealing a possible involvement of central sodium detection mechanisms in salt-sensitive hypertension. Changes in plasma sodium are detected by specialized osmosensory neurons located in hypothalamic organum vasculosum lamina terminalis (OVLT) and supraoptic nucleus (SON). Under normal physiological conditions, increased plasma sodium causes activation of these neurons and release of vasopressin (VP), antidiuretic hormone that mediates water retention by the kidney and vasoconstriction, to achieve body fluid homeostasis. Chronic exposure to HDS is associated with excessive activation of VP neurons, causing a VP-mediated increase in blood pressure. The molecular mechanisms underlying excessive secretion of VP in HDS are not fully understood. Osmosensory neurons harbor unique cytoskeleton networks comprised of a subcortical actin layer and somatic scaffold of interweaved microtubules, regulating the sensitivity of neuronal activation. Chronic exposure to HDS increases the density of actin and microtubules in osmosensory neurons. mDia1 is the major direct downstream effectors of RhoA, mediating its effects on actin and microtubule polymerization and stability. Our data suggest that mDia1 is elevated in the OVLT and SON following HDS. We hypothesize that chronic exposure to HDS causes an activation of the RhoA-mDia1 pathway to increase the cytoskeletal density in osmosensory OVLT and VP neurons, leading to excessive VP secretion, volume expansion, elevated blood pressure, and hypertension.

Ondansetron, a highly-selective 5-HT₃ receptor antagonist, alleviates L-DOPA-induced dyskinesia in the 6-OHDA-lesioned rat model of Parkinson's Disease

A-14

Cynthia Kwan*, Dominique Bédard, Imane Frouni, Adjia Hamadjida, Philippe Huot

L-3,4-dihydroxyphenylalanine (L-DOPA) therapy remains the mainstay treatment for Parkinson's disease (PD). However, long term use leads to motor complications such as dyskinesia in approximately 50-95% of patients with PD. Previous studies have shown that antagonism of the serotonin type 3 (5-HT₃) receptor reduces dopamine levels within the basal ganglia, which characterizes the dyskinetic state. We hypothesized that 5-HT₃ receptor blockade would be a new therapeutic strategy to alleviate dyskinesia. Here, we determined the effect of the highly-selective 5-HT₃ antagonist ondansetron on L-DOPA-induced dyskinesia in the 6-hydroxydopamine (6-OHDA)-lesioned rat. Following assessment of the degree of parkinsonism by the cylinder test, two sets of experiments were then conducted. In the first set, rats were primed with L-DOPA to induce axial, limbs and orolingual (ALO) abnormal involuntary movements (AIMs), after which ondansetron (vehicle, 0.0001, 0.001, 0.01, 0.1 or 1 mg / kg) was administered in combination with L-DOPA. In the second set, rats were administered ondansetron 0.0001 mg/kg or vehicle, started concurrently with L-DOPA, once daily for 22 days, during which the severity of ALO AIMs was regularly monitored. After a washout, an L-DOPA challenge was administered and ALO AIMs severity was assessed. The effect of ondansetron on L-DOPA anti-parkinsonian action was also determined by the cylinder test. The addition of ondansetron 0.0001 mg/kg to L-DOPA resulted in a significant reduction of ALO AIMs duration and amplitude, by 53% and 51%, respectively (both $P < 0.01$), when compared to vehicle. Ondansetron 0.0001 mg/kg, when started concurrently with L-DOPA, also attenuated ALO AIMs amplitude by 41% ($P < 0.001$), when compared with L-DOPA/vehicle. The anti-dyskinetic effect of ondansetron was achieved without impairing L-DOPA anti-parkinsonian action. These results suggest that selective 5-HT₃ receptor blockade is a novel and effective therapeutic approach to reduce the severity of dyskinesia and to attenuate its development.

Amygdala and thalamic inputs to the nucleus accumbens similarly regulate feeding and reinforcement

A-15

C.K. Lafferty*, S.R. Reed, J.A. Mendoza, A.K. Yang, J.P. Britt

Excitatory inputs to the nucleus accumbens (NAc) encode features of reward-associated cues and motivational state. The specific information encoded in amygdala and thalamic inputs is unclear, but recent studies suggest these pathways have opposing influences on behaviour. To better understand NAc information processing and input-specific function, here we compare manipulations of these two pathways on behaviours highly sensitive to NAc activity. We report that amygdala and thalamic input-specific manipulations in mice produce comparable changes in behaviour on a range of tasks. Photo-inhibition of either input increases free food consumption as well as effortful reward seeking, particularly during periods of cued reward unavailability. Activation of either input abruptly terminates consummatory behaviour, and both inputs robustly support intracranial self-stimulation. These data suggest that glutamatergic drive, irrespective of source, is a main determinant of NAc behavioural control. Disruptions in NAc glutamate input both motivate unproductive reward seeking and increase feeding.

NMDA receptor elevation of cytosolic reactive oxygen species strengthens GABAergic signaling

A-16

Erik A. Larson*, Michael V. Accardi, Ying Wang, Martina D'Antoni, Benjamin Karimi, Tabrez J. Siddiqui, Derek Bowie

In recent years there have been new advances towards understanding the nature of inhibitory signaling in the brain. Previous work has shown a novel mechanism for strengthening of inhibitory GABAergic signaling by cytosolic reactive oxygen species (ROS) elevated by insulin signalling. Whether GABAergic synapses can also be potentiated by ROS generated by excitatory neurotransmission has yet to be examined. To investigate this question, we performed whole-cell electrophysiological recordings from molecular layer interneurons of the mouse cerebellum. Additionally, we placed an extracellular stimulating electrode in the molecular layer of the cerebellum to activate a network of excitatory parallel fibers (PFs) from granule cells and neighbouring inhibitory interneurons. As anticipated, high frequency activation stimulation of PFs activated extrasynaptic NMDARs which led to elevated cytosolic ROS. This in turn caused a time-dependent increase in the strength of GABAergic synapses. The use of pharmacological blockers suggest that the origin of ROS generated by NMDAR activation is due to the combined activities of neuronal nitric oxide synthase and neuronal NADPH oxidase. Taken together, our data reveal a novel mechanism for the strengthening of GABAergic transmission through a NMDAR-ROS mediated pathway.

What the tad eye tells the tad brain

Vanessa Li*, Anne Schohl, Edward S. Ruthazer

A-17

Topographic maps, one of the most common manner of organization for sensory information in the brain, are believed to undergo an activity-dependent refinement process in development. Mechanisms of this process have been extensively examined at the single or multi-unit level; but to date few studies addressed the emergence of topographic maps at a population scale. My project focuses on the developing *Xenopus laevis* retinotectal system, visualizing the topographic map in the tectum neuropil of albino *Xenopus* larvae with an optical method based on in vivo two-photon calcium imaging. By microinjecting messenger RNA for the genetically-encoded calcium indicator GCaMP6s into one blastomer of two-cell stage *Xenopus* embryos, we can obtain tadpoles with fluorescent protein expression restricted to half the animal. Since retinal ganglion cell projections crosses the midline, this approach permits the presynaptic terminals of RGC inputs and the postsynaptic dendritic fields of tectal neurons to be observed independently. We then present monocular visual mapping stimuli while performing calcium imaging on the tadpole brain, the correlation of fluorescence intensity changes to visual stimulus location allowing us to extract retinotopic maps for both azimuth and elevation. We proceed to quantify global features of the maps, such as the layout of the topographic gradient, and compare maps in individuals at different developmental stages and under influence of different developmental factors. Our results complement the current literature of longitudinal studies on map emergence with whole-circuit observations, and provide valuable insight to developmental priorities in the presynaptic and postsynaptic components of the tectal circuitry.

Is protein synthesis required for the late phase of netrin-1 induced synaptic potentiation?

A-18

Jeanne F Madranges*, Stephen D Glasgow, Edward S Ruthazer,
Timothy E Kennedy

Long-term potentiation (LTP) is an activity dependent form of plasticity that strengthens glutamatergic synapses and serves as a cellular model of learning and memory formation. We have recently demonstrated that netrin-1, a secreted chemotropic cue that regulates cell migration, axon guidance and synaptogenesis during neural development, is required and sufficient for LTP at the Schaffer collateral synapse through rapid recruitment of GluA1 AMPA receptors. Previous findings indicate that netrin-1 can rapidly initiate protein synthesis through local translation in neurons, suggesting that netrin-1 may regulate long-term changes in synapse strength through translation of synaptic proteins. Here, we demonstrate that transient bath application of netrin-1 results in a persistent potentiation of synaptic responses for >3.5 hours in adult hippocampal brain slices, indicating that netrin-1 induced synaptic strengthening is long-lasting. Investigating a role for translation, our findings suggest that the long-lasting synaptic plasticity induced by netrin-1 requires de novo protein synthesis.

Structure-function relationships underpinning brain-specific Nav1.5 voltage-gated sodium channels

A-19

Adamo S. Mancino*, Yuhao Yan, Mark R.P. Aurousseau, Derek Bowie

The voltage-gated sodium channel Nav1.5 is studied mainly for its contribution to the cardiac action potential. However, there is growing evidence to suggest that 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/mH1 retains exon 6b while 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/mH1. The two splice-variants differ at 7 amino acid residues, all of which are located in the voltage sensor domain (VSD) 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. Here, we engineered single point mutations, introducing key amino acids from Nav1.5e into Nav1.5/mH1 and vice versa, and identified that two important amino acid switches, aspartate-lysine at position 211 and threonine-serine at position 207, are responsible for the altered gating profile. We speculate that these exchanges alter the network of counter-charges in the domain I VSD as a mechanism of action. Furthermore, in order to examine the relative contribution of each domain to the activation process, we neutralized the gating charges across each domain and noticed that domain I VSD is the major determinant, lending insight into why splicing evolved in domain I. 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.

Genetic, environmental and child characteristics as moderators of the relationship between prenatal depression and early child internalizing problems

A-20

Carley Marshall*, Sahar Balvardi, Cathryn Gordon Green, Leonora King, Eszter Szekely, Ashley Wazana

Background exposure to prenatal maternal depression is associated with the development of child psychopathology, including a heightened risk for both externalizing and internalizing problems. An understanding of moderators of risk would elucidate developmental models and inform strategies for early identification and prevention. Method Articles were searched for using the Medline database with no limitation on publication date. Abstracts were examined for relevance by one reviewer and the papers were retrieved if original data was presented on the moderation of prenatal maternal depression in the prediction of childhood internalizing pathology before the age of 5. Data was extracted from the identified articles by one reviewer. The results are summarized in a tabular and narrative review which structures identified moderators by biological and genetic, environmental and social factors, and child characteristics, such as temperament and gender. Results The effect of the following moderators are presented: biological susceptibility including candidate genotypes and genetic risk scores; environmental, such as parenting styles (intrusive, over controlling), level of father involvement (presence, time spent with the child), the type of maternal care; psychological factors, including attachment (insecure attachment); socioeconomic status and positioning, including maternal education and SES, as well and child gender and temperament. Greatest evidence at this time points to an important moderating role of maternal care and attachment. Conclusion Moderators are regularly lacking from predictor models of prenatal maternal depression. The separate effect of prenatal and postnatal depression are also inconsistently disentangled. There is a small literature available specifically predicting anxiety or depression in preschool-aged children. Inclusion of moderators would support efforts to explain inconsistencies in the literature pertaining to the development internalizing problems among this age group.

An investigation of Wnt3a as a multifunctional retrograde cue in retinotectal circuit development

A-21

Ryan McPhedrain*, Stephen Glasgow, Edward S. Ruthazer

Wnts are ubiquitous intercellular signalling molecules which regulate a multitude of homeostatic, developmental and synaptic processes. Dysfunction of Wnt signalling has been associated with a variety of neurodevelopmental and neurodegenerative disorders. Understanding the functional roles of Wnt signalling and how they are regulated may provide important insights into the mechanisms underlying these disorders. Using albino *Xenopus laevis*, this research aims to characterize the role of Wnt3A in modulating axonal branch dynamics and synaptic physiology in the developing retinotectal circuit. Evidence suggests that disruption of Wnt signalling in presynaptic retinal axon terminals through the downstream effector dishevelled (Dsh) increases the number of axonal branches while promoting a slight elevation in arbor length. Furthermore, electrophysiological analysis of spontaneous and miniature excitatory postsynaptic currents (EPSCs) was performed to evaluate the acute and chronic effects of Wnt3A signalling. This research suggests Wnts regulate axonal branch dynamics and synaptic efficacy, which may have implications for mechanisms underlying neurodegenerative disease.

Phasic dopamine signaling communicates both a retrospective and a prospective learning signal

Jesse Mendoza*, Christopher Lafferty, Angela Yang, Jonathan Britt

A-22

Reinforcement learning provides a formulation through which an agent can refine its behaviour as to maximize reward. The dopamine neurons originating in the ventral tegmental area (VTA) are believed to convey a reward prediction error (RPE) required by reinforcement learning. By construction, an RPE is inherently retrospective, adjusting the values of states and actions preceding it. However, dopamine may also convey a prospective signal during the onset of a predictive cue by invigorating reward-seeking behaviour and possibly communicating the expected value of the current state. In the present study, we wished to evaluate whether the dopamine signal adjusts action value retrospectively, prospectively, or by both means. Mice were trained on forced trials, in which a single lever was presented, and choice trials, wherein both levers were presented. Operant responding in all conditions resulted in the delivery of the same sucrose reward. If dopamine communicates a prospective signal of expectations, then alterations in dopamine signaling during the cue onset, in this case the lever presentation, should result in an RPE upon reward reception and would subsequently adjust action value for that lever. Interestingly, we find that both optogenetic stimulation and inhibition of VTA dopamine neurons during forced trial presentations of a specific lever reduced choice preference for that lever. In contrast, optogenetic manipulations of VTA dopamine neurons during consumption in rewarding forced trials of a specific lever bidirectionally induced a choice bias and altered performance for that lever. Together these findings demonstrate a retrospective and prospective role of dopamine signaling in action value adjustments, however it does not appear to be a result of mediating expectations.

IgSF21-Neurexin2a complex regulates inhibitory synapse development

A-23

Yusuke Naito*, Yuko Tanabe, Cristina Vasuta, Alfred Lee, Youssouf Soumounou, Michael Linhoff, Hideto Takahashi

GABAergic 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. 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 complexes, called synapse organizing complexes. These complexes have been demonstrated as essential molecular signals for synapse development. Although many synapse organizers have been identified to induce excitatory synapses, few synapse organizers selective for inhibitory synapse development have been isolated.

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 Neurexin2 α (NRX2 α) as an IgSF21-interacting presynaptic organizer. Interestingly, IgSF21 selectively binds to NRX2 α but not any other NRX isoforms and recruits NRX2 α to presynaptic sites in a trans-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 NRX2 α and that this is essential for normal brain function.

Make Electrophysiology Great Again (MEGA)

Konstantinos Nasiotis*, Martin Cousineau, Francois Tadel, Adrien Peyrache, Christopher C. Pack, Sylvain Baillet

A-24

The methods for electrophysiology in neuroscience have evolved tremendously over the recent years, with a growing emphasis on dense-array signal recordings, often at multiple sites simultaneously. Our goal was to implement a software that is oriented for basic electrophysiology, with a user-friendly graphical interface that allows a user experience that interacts as little as possible with "what is under the hood" unless it is explicitly needed. We introduce a free, open-source software application for integrated and advanced data analytics and visualization in basic e-phys. This tool responds to an unmet need of the large neuroscience community relying on diverse recording techniques, ranging from in vitro slices to free-behaving models. The core notion is that researchers (even without any programming skills) shall rely on a tool in which they can import a raw version of their experimental data and then perform all data analytics (spike sorting, spike analysis, LFP analysis etc.) in a traceable (logged) and reproducible manner.

Amyotrophic lateral sclerosis models of CHCHD10 in zebrafish

A-25

Virginie Petel Légaré*, Ziyaan Harji, Esteban Rodriguez Pinto, Gary Armstrong

OBJECTIVE: To investigate the cellular and pathophysiological consequences of the analogous zebrafish (*Danio rerio*) *chchd10* variants: P83L, A35D, and S60L in vivo. **BACKGROUND:** Recently, dominantly inherited missense mutations in the nuclear encoded gene CHCHD10 (encoding the mitochondrial protein CHCHD10) were identified in both sporadic and familial amyotrophic lateral sclerosis (ALS) cases, implicating mitochondrial dysfunction in the pathogenesis of this disease. The mechanism of pathogenicity of mutations in CHCHD10 is unknown, yet loss of the CHCHD10-CHCHD2 complex has been proposed to lead to altered cellular respiration. We hypothesize that this could affect mitochondrial content and function at the neuromuscular junction (NMJ), a site that is particularly impaired in ALS. **METHODS:** Knockin (KI) and knockout (KO) *chchd10* models will be generated using the CRISPR/Cas 9 mutagenic system. Motor phenotypes will be characterized using motor tracking software. Quantitative PCR (qPCR) will be used to determine altered gene expression. Finally, co-localization between pre- and post-synaptic markers of the NMJ by immunohistochemistry, and metabolic capacity, will be characterized permitting a more thorough understanding of the cellular basis of the disease. **RESULTS:** A KO model was identified in one of our founder lines. Loss of *chchd10* led to reduced survival at the larval stage as well as a reduction in mean locomotor velocity when compared to wild type (WT) siblings. qPCR data revealed a significant increase in *chchd2* transcript expression at larval stages. **DISCUSSION:** The data generated supports the loss of function hypothesis, and a potential compensatory role of *chchd2* in animals lacking *chchd10*. Further studies will be performed to determine the effect on oxidative metabolism, and NMJ function.

Efficient radiosynthesis and preclinical evaluation of [18F]fluoro-GW2580 as a PET tracer for Trk receptor imaging

A-26

Thomas A. Singleton*, Hussein Bdair, Arturo Aliaga, Pedro Rosa-Neto, Ralf Schirmacher, Vadim Bernard-Gauthier, Alexey Kostikov

Tropomyosin receptor kinases TrkA/B/C regulate neuronal differentiation, growth, and survival via their interactions with neurotrophin factors. Downregulation of Trk receptors has been reported in many pathological conditions of the central nervous system (CNS), including stroke, traumatic brain injury and a wide spectrum of neurodegenerative conditions, such as Alzheimer's disease (AD) and others. Recently, several radioligands targeting Trk receptors for in vivo imaging by means of positron emission tomography (PET) have been developed and evaluated in preclinical and clinical settings. However, all of those tracers are based on type-I DFG-in binding Trk inhibitors, characterized by fast on and off kinetics, which result in a relatively rapid washout from the target tissue and relatively low specific binding. Here we present an efficient radiolabeling and preclinical evaluation of [18F]fluoro-GW2580, a type-II DFG-out binding inhibitor PET tracer candidate for Trk receptor imaging, which is hypothesized to display a more favourable off rate and reduced endogenous competition with ATP leading to higher specific binding. We have successfully optimized the radiosynthesis of this tracer from a previously-reported four-step sequence to a one-step copper-catalyzed 18F-labeling of a boronate-functionalized precursor, which allows for production of high doses of [18F]fluoro-GW2580, suitable for preclinical and eventually clinical PET imaging. Following HPLC purification, [18F]fluoro-GW2580 was obtained in high radiochemical and chemical purity, injected into rats for microPET imaging and evaluated in autoradiography experiments using rodent and human brain sections. The tracer exhibits good binding properties in vitro with ubiquitous binding in line with pan-Trk CNS expression. MicroPET studies revealed brain permeability of [18F]fluoro-GW2580 in rodents (whole brain SUV_{max} = 0.75) and moderate washout as expected. Experiments currently in progress aim to demonstrate the selectivity and specificity of the [18F]fluoro-GW2580 binding by blocking studies with various Trk receptor ligands.

Chronic pain after scoliosis surgery in adolescents: A longitudinal study exploring the role of neuroplastic changes in pain processing

A-27

Alisson R. Teles*, Jean A. Ouellet, Catherine E. Ferland

INTRODUCTION: Chronic pain after surgery for adolescent idiopathic scoliosis (AIS) remains poorly understood. In this exploratory study, we investigated the role of neuroplastic changes in pain sensitivity and modulation on long-term self-reported pain outcomes. **METHODS:** A total of 45 adolescents with idiopathic scoliosis were included in this longitudinal study. Patients were evaluated in 5 time-points (1 week before surgery, 5 days, 6 weeks, 6 months, and 1 year after surgery) with QST and validated questionnaires (NRS of pain, SRS30, pain catastrophizing scale-PCS). A total of 6 QST parameters were assessed: pain pressure threshold at a non-painful control site (PPTforearm) and at the back (PPTback), heat pain threshold (HPT), cold pressor test (CPT), temporal summation of pain (TSP), and conditioned pain modulation (CPM). The SRS30 pain domain at 1year was used to identify high and low pain levels (cutoff = 3.5). Linear mixed-effects models were used to assess changes over time in QST variables between groups (low x high level pain), with a random intercept used to control for the repeated measures for each individual with a time point and over time. Models were adjusted for sex. Initially, we looked for the presence of a significant interaction between time and group. In models with significant interaction, the groups were compared in each time point using the Tukey pairwise multiple comparisons. If no significant interaction was observed, the interaction term was removed and the main effect of time and group was tested in order to verify significant changes over time adjusting for group or a significant difference between groups after adjusting for time. **RESULTS:** A significant interaction between time and group was identified for HPT ($p = 0.030$). In the low pain group, a significant increase in HPT (less heat pain sensitivity) was observed at 1 year in comparison with the other time-points ($F = 10.92$, $P < 0.0001$); no significant difference was observed in the high pain group ($F = 1.77$, $P = 0.145$). After controlling for PCS, the interaction time X group remained statistically significant. No significant interaction between time and group was observed in the remaining 5 QST parameters ($P > 0.05$: PPTforearm, PPTback, CPM, CPT, TSP). A significant main effect of time was observed in PPTforearm ($P = 0.021$), PPTback ($P < 0.0001$), CPT ($P = 0.022$), and CPM ($P = 0.015$), meaning that a significant change over time was detected in those parameters after adjusting for groups. **CONCLUSIONS:** Significant neuroplastic changes in pain sensitivity and modulation were observed in this longitudinal study. A significant increase in HPT from 6m to 1y was identified in the low pain level but not in the high pain level group, suggesting the potential contribution of neuroplastic changes in pain sensitivity on postsurgical pain outcomes.

Functional resting state connectivity of impulsivity, sensation-seeking, body Mass, age and sex in emerging adults

A-28

Maria Tippler *, Rachel J Sharkey, Sylvia Cox, Natalia Jaworska, Kevin Larcher, Yu Zhang, Ayca Altinkaya, Abbas Sadikot, Bratislav Misic, Sophie Parent, Natalie Castellanos-Ryan, Frank Vitaro, Michel Boivin, Richard Tremblay, Chawki Benkelfat, Alain Dagher, Jean Séguin, Marco Leyton

INTRODUCTION: Emerging adulthood is a period characterized by rapid neurodevelopmental and contextual changes. It also commonly marks the onset of illnesses such as substance use and eating disorders. Risk factors for these problems include sensation seeking (SS), impulsivity (IMP), body-mass index (BMI) and mesolimbic pathway function. Based on our findings in a separate cohort of young adolescents, we investigated the effects of these risk factors on resting-state functional connectivity profiles in emerging adults. **METHODS:** Participants were 57 volunteers from a longitudinal birth cohort (age 18.5 ± 0.6 , 23 males). Collected data included resting-state functional scans (3T, Siemens), SS and IMP scores from the Substance Use Risk Profile Scale, BMI, age and sex. As in our previous study, a partial least squares correlation method analysis of seed-based brain-wide connectivity was performed with the following regions of interest: bilateral sub-thalamic nucleus (STN), ventral striatum (VS), ventral tegmental area (VTA) and substantia nigra (SN). To identify the most strongly loaded brain regions, bootstrap ratios for the brain regions were thresholded at $z = \pm 3$. Stability testing was conducted with 75% of the sample chosen at random, repeated 100 times. Since most results were arbitrarily negatively directional, all results were multiplied by -1 for ease of interpretation. **RESULTS:** A single latent variable was derived from the input of the five characteristics (SS, IMP, BMI, age and sex) and whole-brain connectivity of the four bilateral seeds ($s = 7.43$, $p = 0.0055$), a result that survived stability testing. SS and IMP scores, BMI, and female sex loaded positively with the latent variable, while age loaded negatively. The latent variable primarily reflected connectivity of the VTA, SN, and STN to multiple other brain regions. Correlations between seed-regional connectivity and the latent variable that surpassed the threshold included parts of the basal ganglia, limbic areas, the cerebellum, biogenic amine cell body regions and motor nuclei. **DISCUSSION AND CONCLUSIONS:** Based on the characteristics directionality loading with the latent variable, emerging adults with higher SS, higher IMP, higher BMI, younger age and female sex show greater connectivity between the seeds and multiple brain regions. Some of these brain regions overlapped with our previous study yet differed also with more limbic sites as seen in the younger adolescents. Together, these networks might contribute to the integration of mood, motivation and motor output and their evolving regulation during maturation.

Genetic assessment of the Kirrel combinatorial code in olfactory map formation

A-29

Neelima Vaddadi*, Katrine Iversen, Reesha Raja, Alina Phen, Alexandra Brignal, Jean-François Cloutier

The formation of complex stereotypic connections between olfactory sensory neurons (OSNs) and second order neurons in the olfactory bulb (OB) is important for accurate odorant information processing. While axon guidance cues direct the growth of OSN axons to broad regions of the OB, the combinatorial expression of cell surface molecules that promote axonal adhesion, such as the Kirrel family of proteins, have been proposed to regulate the coalescence of OSN axons into specific glomeruli. While Kirrel2 and Kirrel3 are differentially expressed in populations of OSNs and their overexpression in MOR28-expressing neurons leads to improper targeting of these axons, their requirement for the coalescence of OSN axons remains to be established¹. To assess the function of Kirrel2 and Kirrel3 in the coalescence of OSN axons into specific glomeruli, we have examined the targeting of multiple populations of OSN axonal projections in different regions of the OB in mice bearing loss of function ablations of the Kirrel2 and Kirrel3 genes. These analyses revealed that ablating expression of Kirrel2 and Kirrel3 in the S50 and MOR1-3 populations of OSNs that innervate the DI region of the OB did not alter the targeting and coalescence of their axons. In contrast, loss of Kirrel2 in M72 and MOR174-9 OSNs that innervate the DII region of the OB results in the formation of ectopic glomeruli in the OB, indicating that Kirrel2 is necessary for the coalescence of these axonal populations. Interestingly, the combined loss of Kirrel2 and Kirrel3 in MOR28 OSNs that innervate the most ventral region of the OB did not alter the coalescence of these axons. Our results uncover a differential requirement in OSN population for a Kirrel combinatorial code in axonal coalescence and indicate that additional families of cell adhesion molecules likely contribute to the coalescence of OSN axon populations in some regions of the OB.

Genomic anatomy of the human hippocampus informs interactions with the brain in health and disease

A-30

Jacob W. Vogel*, Renaud La Joie, Alexandr Diaz-Papkovich, Michel Grothe, Claude Lepage, Yasser Iturria-Medina, Gil D. Rabinovici, Alan C. Evans

The longitudinal (anterior-posterior) axis represents one of the principal dimensions of functional and anatomical organization of the human hippocampus. Several studies have identified fairly consistent patterns of gene expression that explain the homologous longitudinal (dorsal-ventral) axis of the rodent hippocampus, but no studies to date have identified differential gene expression patterns that regulate the longitudinal axis of the human hippocampus. In pursuit of these patterns, we apply a machine learning model to the expression patterns of 50,000 genes within 170 tissue samples extracted from the hippocampus of six human donors as part of the Allen Human Brain Atlas. Using only gene expression patterns, our LASSO-PCR model explained 87% of the variance in the position of samples across the longitudinal axis, and predicted 67% of the variance in the position of unseen samples. Back-propagating the model weights revealed the majority of the variance to be explained by the expression profile of <200 genes. Unsurprisingly, many of these genes were well-established regulators of neural tissue development and cell-migration, but the analysis also revealed a differential distribution of certain neurotransmitter receptors and other synaptic proteins across the longitudinal axis. We created a Hippocampal Axis Genomic Similarity (HAGS) index characterizing patterns of genomic similarity between the samples and the anterior or posterior hippocampus, and applied this index to an additional 1600 extra-hippocampal samples across the cortex, brainstem and cerebellum. A basic pattern emerged across the entire brain such that the brainstem and antero-ventral cortical regions showed similar gene expression patterns to the anterior hippocampus, while the cerebellum and postero-dorsal cortical regions showed similar patterns to the posterior hippocampus. The HAGS index alone could differentiate frontal from occipital lobe samples with 84% accuracy, and brainstem from cerebellum samples with 92% accuracy. A brain region's HAGS index was associated with that region's preferential functional and structural connectivity to the anterior or posterior hippocampus; to the region's differential vulnerability to Alzheimer's disease or frontotemporal dementia; and to the region's differential involvement in cognitive networks associated with the anterior or posterior hippocampus. Altogether, our findings suggest a general organizational axis of the human brain, where an anterior-ventral - posterior-dorsal gradient emanates from the hippocampus and explains regional involvement in diverse behaviors, underscored by a specific pattern of gene expression. These findings together form a template for studying how specific genes regulate the development of these systems and their involvement in specific behaviors and, potentially, specific diseases.

Elucidating the role of 4EHP and GIGYF2 in Autism Spectrum Disorder

Shane Wiebe*, Argel Aguilar-Valles, Nahum Sonenberg

A-31

Autism Spectrum Disorder (ASD) is a neurodevelopmental and cognitive disability that affects millions of individuals worldwide. It is primarily characterized by three core deficits: impaired social interaction, lack of verbal and nonverbal communication, and repetitive or restrictive behavior such as hand flapping and self-injury. The etiology for the majority of ASD cases is unknown, but genetic studies have revealed that the heritability of ASD is high (0.6-0.9) with more than 300 genes linked to the disorder. Clusters of genes encoding proteins of common cellular functions are being identified, such as structural synaptic proteins and regulators of mRNA translation. The eukaryotic initiation factor 4E homologous protein (4EHP) binds to the mRNA 5'-cap and acts to repress translation. Although its mechanism of action is not fully understood, 4EHP forms a protein complex with GIGYF2 which is required for the stability of both proteins. Since numerous mutations in GIGYF2 have been linked to ASD, we hypothesized that the function of 4EHP and GIGYF2 is important in regulating neurodevelopment and susceptibility for ASD. To this end, we generated 4EHP and GIGYF2 double heterozygous mice and tested them for autistic-like behaviors. These animals displayed normal repetitive and social behavior, possibly due to haplosufficiency. We therefore employed a conditional knockout model where 4EHP is deleted in EMX1-expressing cells with a concomitant reduction in GIGYF2. These mice have an impaired preference for social novelty suggesting a developmental or cell-type specific role for 4EHP and GIGYF2 in regulating social behavior. Future work will elucidate which mRNAs are regulated by 4EHP-GIGYF2 and how their dysregulation affects neuronal development and synaptic function.

Native GluA2-containing AMPA receptors are calcium-permeable in the presence of auxiliary proteins

Yuhao Yan*, Ingrid Osswald, David M Maclean, Derek Bowie

A-32

Ca²⁺ influx through ionotropic glutamate receptors (iGluRs) in synapses is crucial in mediating fundamental cellular processes found in neurons such as long-term potentiation (LTP). It has been generally assumed that synaptic Ca²⁺ influx is dominantly mediated through NMDA receptors (NMDAR), largely because of their high permeability to Ca²⁺ and the low abundance of calcium-permeable AMPA receptors (CP-AMPA) in most synapses. Here we show that AMPARs can also contribute to Ca²⁺ influx independent of NMDAR in certain cell types in mouse retina, cerebellum and hippocampus. Surprisingly, a subpopulation of these CP-AMPARs are philanthotoxin and IEM insensitive. Such pharmacological profile suggests that this subpopulation consists mainly of GluA2-containing AMPARs, which goes against previous assumptions that GluA2-containing AMPARs are calcium impermeable. In heterologous expression system, we show that GluA1/A2 heteromers alone do not permeate calcium; however, the presence of auxiliary proteins, namely TARPs and Cornichon-3 (CNIH3), render them calcium-permeable. This finding provides yet another molecular mechanism of how synaptic Ca²⁺ influx as well as downstream cellular pathways can be regulated.

Grid cells, head direction cells, and border cells: Characterization of egocentric and allocentric spatial navigation in a mouse model of Alzheimer's disease

A-33

Johnson Ying*, Alexandra Keinath, Mark P. Brandon

Alzheimer's disease (AD) is a neurodegenerative disease characterized by spatial memory impairments in the form of 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. We demonstrate that grid cells are disrupted in aged J20 animals (months 5-7). Network-level impairments of non-classified cells in the MEC are detectable in young J20 animals (months 2-4), preceding the formation of plaques. To corroborate our physiological findings, we aimed to better characterize the nature of spatial memory impairment seen in AD and to propose a function for the MEC in navigation and memory. J20 mice were tested in a path integration food-foraging task in darkness where they must integrate self-motion cues such as heading direction and movement speed to continuously update their perceived location in space. Without allocentric visual cues, this task provides an opportunity to characterize the classic navigational deficits seen in AD patients as well as the role of specific MEC cell types in navigation. Our preliminary data show that aged J20 mice demonstrate impaired path integration behaviour which correlates to the observed physiological dysfunction. Overall, our results suggest that grid cells in the MEC are important targets for future therapies to restore spatial cognitive function in human AD patients.

SESSION 'B'

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September 21 2018: 13:25 – 15:15

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In-vivo rodent studies with [11C]UCM765, a putative tracer for imaging of MT2 receptor by PET

B-01

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Melatonin is a neurohormone, dubbed the hormone of darkness, mainly synthesized by the pineal gland during the dark period of light-dark cycle. Melatonin is known to modulate a wide variety of physiological functions in mammals, such as circadian rhythms, mood, reproduction, immune and cerebrovascular functions. Melatonin-mediated responses occur through the activation of at least two high-affinity G protein-coupled receptors, known as melatonin receptors type 1 and 2 (MT1 and MT2). We herewith report in vivo studies with [11C]UCM765, a first-in-kind carbon-11 radiolabelled PET tracer that targets MT2 receptors ($pK_i = 10.18$). Preclinical PET studies with [11C]UCM765 in rats (Sprague Dawley) revealed a rapid tracer penetration through the blood-brain barrier, followed by a fast washout from the brain. Excessive extracerebral tracer uptake was also observed in Harderian glands that express high levels of MT2 receptors. To explore the tracer selectivity, cerebral and extracerebral uptake of [11C]UCM765 was challenged via prior subcutaneous administration of 10 mg/kg 4P-PDOT, a selective MT2 receptor antagonist, or 150 mg/kg melatonin. In addition, non-radioactive UCM765 was concurrently administered with the radioactive counterpart in a self-blocking experiment to examine the tracer specificity. These blocking experiments revealed a modest reduction in the brain uptake of [11C]UCM765, indicating that the tracer exhibits selectivity to MT2 receptors. Our findings warrant further investigations of the role of MT2 receptors in animal models of human diseases.

Changes in laterality of spinofugal projections caused by spinal cord deletion of DCC during development

B-02

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Sensory information from the body channeled via spinal projection neurons (SPNs) to supraspinal centres generates appropriate motor responses. A significant number of SPNs are commissural such that their axons cross the spinal midline to innervate contralateral targets in the brain. The identity of axon guidance cues that orchestrate midline crossing and the development of spinofugal connections is unknown. We have recently shown that DCC, the netrin-1 receptor, is required for the development of the spinothalamic tract in mice. However, the role of DCC in guiding other classes of SPNs is unknown. First, we characterised the identity of SPNs that express the spinal cord-specific Cre driver *Hoxb8::Cre* via a Cre-dependent axonal TdTomato reporter. Subsequently, we performed a series of anterograde tracings via spinal cord injection of virally-driven synaptic-bound eYFP of spinal cord-specific *Dcc* knockout mice (*Hoxb8::Cre; DCC[flox/-]*) and their control littermates. Here, we demonstrate that in addition to the spinothalamic connections, the commissural nature of spinoreticular and spinomesencephalic tracts is also altered. In control animals, most observed synapses of such projections are contralateral to the spinal injection. In contrast, in *Hoxb8::Cre; DCC[flox/-]* mutants, eYFP signal is increased in the ipsilateral brain targets. Collectively, our results suggest that many SPN classes rely on DCC for crossing the nervous system midline before reaching their brain targets.

The developmental connectome of melanopsin-expressing retinal ganglion cells

B-03

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Intrinsically photosensitive melanopsin-positive retinal ganglion cells (OPN4+ ipRGCs) are the earliest born light-responsive cells in the mammalian retina. They are central to the regulation of circadian rhythms and pupillary light reflex. In adults, their connectivity patterns and visual behavioral roles have been well categorized, but this remains unexplored in the developing retina. To fill this knowledge gap, we propose to characterize the connectome of ipRGCs in the first postnatal week in mice. To do this, we will infect OPN4+ ipRGCs with an EnvA-pseudotyped G deleted and GFP expressing rabies virus by injection in either the suprachiasmatic nucleus (SCN), where ipRGCs send their axons, or the retina, where ipRGC cell bodies are located. Injections will be done at three developmental time-points (P1, P4, and P7) in OPN4-Cre:Rosa-TVA-G mice, which will allow specific infection of ipRGCs and retrograde hopping of the pseudotyped rabies virus to reveal connecting partners. Our preliminary work has established the efficacy and specificity of pseudotyped and unpseudotyped G deleted rabies virus in vitro using HEK-293 and HEK-293-TVA-G expressing cells. In addition we have performed viral injections in SCN of OPN4-Cre:ROSA-TVA-G mice at postnatal days 1, 4 and 7. Initial analysis at postnatal day 1 has revealed a large number of Müller glia labelled with GFP, suggesting connections between ipRGCs and Müller glia at this stage. Further investigations will characterize the full repertoire of ipRGC-connecting cell types in the retina during the first postnatal week.

Screening for new effectors of Ephrin-B:EphB2 and Netrin:Unc5c signaling

Chao Chang*, Sylvie Lahaie, Daniel Morales, Artur Kania

B-04

Ephrin-B:EphB2 and Netrin:Unc5c signaling pathways play crucial roles in embryonic development. They are also involved in disorders including Alzheimer's and cancer. While the molecular mechanisms of signaling from EphB2 and Unc5c receptors remain unclear, my study aims to find new intracellular effectors of the two pathways. HeLa cells are a simple cell model for functional studies of EphB2 and Unc5c receptors, shown by our lab and others. In these cells, I used HeLa cells expressing Flag-EphB2 and Flag-Unc5c and AP-MS (Affinity Purification-Mass Spectrometry) to identify potential intracellular interactors of EphB2 and Unc5c receptors. After SAINT analysis, based on the differential spectral counts after ligand treatment, as well as human mutation and animal model phenotypes of the potential interactors, I selected GALECTIN1, MYCBP2, RACK1 and NOTCH2 proteins as potential ephrin-B2:EphB2 signaling effectors, and ROCK1 and NOTCH2 as potential effectors for Netrin1:Unc5c signaling. Interaction assays and functional assays of the potential effectors will be tested in HeLa cells and motor neurons. The study of the confirmed effectors will be expanded to the field of cancer and Alzheimer's.

Fast, high-resolution 3D imaging of live oligodendrocytes in a microfabricated culture system

Daryan Chitsaz*, Timothy E. Kennedy

B-05

Oligodendrocytes (OLs) wrap CNS axons with layers of membrane to form the myelin sheath. This structure provides metabolic support to the axon, mediates some forms of plasticity, and improves action potential efficiency. While OLs can intrinsically ensheath axons, crosstalk between them and neurons regulates myelination as well. Culturing OLs on polymer nanofibers provides a rapid, experimentally accessible system to assay myelination without these confounding axonal factors. Leveraging the speed, resolution, and sensitivity of Airyscan Fast Acquisition Mode, we have optimized an imaging approach to visualize OL cell dynamics at the process and organelle levels as they ensheath artificial nanofibers. In future experiments, these confocal imaging approaches will help illuminate the molecular and cellular mechanisms underlying CNS myelination.

Therapeutic exercise in a mouse model of spinocerebellar ataxia type 6

B-06

Anna Cook*, Sriram Jayabal, Mohini Bhade, Alanna Watt

Spinocerebellar ataxia type 6 (SCA6) is a late-onset polyglutamine expansion disease whereby an extended CAG sequence in the CACNA1A calcium channel gene causes symptoms of ataxia and eventual cerebellar degeneration. Treatment options are limited and the pathophysiology is incompletely understood. We used a knock in mouse model with a pathogenic variant of the CACNA1A gene containing an expanded CAG repeat (84Q) to investigate the pathophysiology of the disease. We have shown that at 7 months these mice display significant deficits in firing precision and frequency of Purkinje cells. Previously, we identified the drug 4-Aminopyrimidine (4-AP) as a potential treatment, with chronic oral administration leading to a partial rescue of SCA6 pathology and complete rescue of Purkinje cell firing precision, with no change in frequency. We wondered whether other treatment avenues could rescue motor deficits in our SCA684Q/84Q mice. Exercise has been shown to have neuroprotective effects in humans and improves motor coordination in several mouse models of ataxias. We investigated whether exercise affected our SCA684Q/84Q mouse model using a program of voluntary exercise and observed a partial rescue of motor behaviour and Purkinje cell abnormalities. In contrast to 4-AP, we found that exercise improved Purkinje cell firing frequency without affecting firing precision. Our results suggest that both Purkinje cell rate and precision deficits contribute to SCA6 pathology, and thus a combination therapy approach may be optimal to improve motor coordination in SCA6.

Characterization of cytokine mediation in prodromal Alzheimer's disease: A neuroimaging study in the TgF344-AD rodent model

B-07

Katrina Cruickshank*, Caitlin Fowler, Jamie Near

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, presenting neuropathologically with amyloid beta plaques and hyperphosphorylated tau tangles, clinically accompanied by progressively declining memory and cognitive function. Although reasonably well characterized in terms of pathology and symptomatology, a means for definitive diagnosis antemortem and effective treatment are lacking. Experimentation in animal models and investigation into alternate pathological hallmarks presents a promising avenue for the development of translational biomarkers and testing of candidate therapeutics. Of interest, a paradoxical increase in neuronal activity during prodromal stages of AD has been observed. This hyperexcitability is hypothesized to trigger the proceeding synaptic and cognitive decline, and may be linked to the proinflammatory cytokine, tumor necrosis factor alpha (TNF). As such, inhibition of TNF has been proposed as a promising therapeutic target. Here, we aim to characterize early neurochemical alterations in aging TgF344-AD rats using magnetic resonance spectroscopy (MRS). Concurrent changes in TNF levels will be assessed using enzyme-linked immunosorbent assays (ELISA). Finally, the effects of acute early treatment with a TNF inhibitor on disease progression will be investigated through further MRS, as well as magnetic resonance imaging (MRI), behaviour and histology. Preliminary data show an increase in myo-inositol, an indicator of glial activation, in 10-month-old TgF344 rats, suggestive of early inflammatory activity, in addition to other pathological neurochemical and cognitive alterations. Further MR analysis, corroborated with behavioural and histological data will provide an avenue to validate potential neurochemical biomarkers of AD, in addition to testing the value of early, acute TNF inhibition as a preventative therapeutic.

Investigating brain functional connectivity in mouse models of neuropsychiatric disorders using fMRI

B-08

Gabriel Desrosiers-Gregoire*, Daniel Gallino, Gabriel Devenyi, Mallar Chakravarty

The functional organization of the brain is characterized by synchronized communication between brain areas through major networks. This topology can be studied through measurements of functional connectivity (FC) using resting-state functional magnetic resonance imaging (fMRI). Although deficits in the integrity of FC have been studied across various neuropsychiatric disorders, very few investigations have been similarly conducted in animal models, due to technical challenges of applying fMRI in small animals, leaving a major translational gap. However, technical progress in the application of fMRI to rodents under anesthesia has allowed the imaging community to obtain increasingly reliable measurements of FC and detection of functional networks in the rodent brain. My research project will consist in developing reliable protocols for fMRI of mice under anesthesia. Given that anesthesia regimens differentially alter measurements of FC, I will compare results obtained from animals anesthetized under isoflurane, dexmedetomidine, or the combination of both at half doses, to determine which regimen offers most reliable measurements while minimizing the influence of anesthesia on FC. Outcomes measures include reliability of detecting major networks across regimes, signal-to-noise ratio, and blood oxygen level dependent signal changes detected under the influence of hypercapnia.

Growth impairment under conditions favoring mitochondrial oxidative metabolism in a yeast model of cancer-associated isocitrate dehydrogenase mutation

B-09

Sophie Fiola*, Eli Ganni, Rita Lo, Elena Kuzmin, Roberto Jose Diaz

The use of the budding yeast *Saccharomyces cerevisiae* as a model system to study cancer allows for faster, more efficient elucidation of various molecular mechanisms, including mutation rate by fluctuation analysis, cell cycle analysis by flow cytometry, metabolism via growth rate analysis, and functional genomics via genomic array screening. The vast majority of low grade gliomas (LGGs) carry somatic mutations in isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2) genes. IDH1 and IDH2 catalyze the oxidative decarboxylation of isocitrate to α -ketoglutarate (α -KG) in an NADP⁺ dependent manner. A point mutation (R132H in IDH1 and R172H in IDH2) confers the neomorphic ability for the enzyme reduce α -KG to D-2-hydroxyglutarate (D2-HG). In *S. cerevisiae*, the NADP⁺ dependent isocitrate dehydrogenases are encoded by three different genes, IDP1, IDP2 and IDP3. We have successfully generated a yeast model that carries the analogous mutation in the yeast IDP1 gene (IDP1R148H). The allele was inserted at the HO locus, which does not alter the endogenous IDP1 gene. In this way, the resulting strain carries both a wild-type and mutant allele of IDP, more closely mimicking the metabolic state of glioma cells. We have validated this insertion by PCR, sequencing, and tetrad analysis. The production of the mutant IDP1R148H protein was detected by Western blot. The IDP1R148H strain shows normal growth on glucose and galactose-containing solid media, but reduced growth on glycerol-containing solid media compared to parental or IDP1WT strains. Impaired growth of yeast when glycerol is the sole carbon source suggests a defect in mitochondrial oxidative metabolism. This observation is consistent with a previous yeast IDP1R148H model which showed extensive mitochondrial DNA loss and respiration defects. Taken together, we have developed an effective model of IDH-mutant LGGs in *S. cerevisiae* that can be further utilized to study molecular mechanisms underlying tumorigenesis of LGGs.

Interneuron populations coordinating locomotor behaviour in *D. melanogaster* larvae

B-10

Alastair Garner*, Jiayi Zhu, Yassine Rahmouni, Tomoko Ohyama

Neural circuit motifs for locomotor behaviours are highly conserved across species. These circuits are hardwired to encode the coordination of behaviour, which encompasses sensory integration, selective motor pool activation and intrinsic motor sequencing. Previous research has revealed circuit mechanisms for motor timing (notably central pattern generators), but less is known about the mechanisms underlying the recruitment of distinct motor ensembles. Recent studies have highlighted the larval fruit fly (*Drosophila melanogaster*) as a powerful model for studying locomotion, as critical circuit nodes sufficient for initiating a stereotyped escape behavior repertoire (bending, rolling and fast-crawling) have already been described. Using this model, we aim to dissect the components of the interneuron circuitry that coordinates escape behaviours. To address this issue, we use optogenetic manipulations in vivo to interrogate the contribution of ventral nerve cord interneurons to behavioural performance. We report the discovery of two lineage-related premotor neuron populations that affect the expression of escape behaviours. Perturbing the function of these neurons induces abnormal behaviour sequencing and suppression of specific components of the behavioural repertoire. We conduct additional behavioural experiments and morphological analysis to further characterise these populations. Our preliminary data suggest that distinct interneuron populations modulate the activity of distinct motor pools during locomotion.

Demystifying the effects of acute cardiovascular exercise on motor learning: A deep learning approach

Arna Ghosh*, Fabien Dal Maso, Georgios D Mitsis, Marie-Hélène Boudrias

B-11

Analysis of Electroencephalography (EEG) data to improve understanding of underlying neural activity is typically hypothesis-driven and requires the investigator to quantify certain features of the EEG time-series. However, this could lead to sub-optimal feature selection. Data-driven approaches like deep learning (DL) allow discovery of the optimal feature set from available data. Convolutional Neural Networks (CNNs) have been recently used for classification tasks in neuroscience. To visualize discriminative features that guide the network's decision, we use a method called cue-combination for Class Activation Map (ccCAM) which is inspired by existing methods in literature and adapted for neuroscience applications. Specifically, a deep CNN architecture, combined with ccCAM is applied on EEG data collected from human subjects to study the effect of exercise on motor learning. Our results reveal discriminative features within specific frequency band (19-31 Hz) that is a subset of the beta-band, which has been found to be significantly modulated by exercise in previous studies. They also reveal that activity in this frequency band propagates across different regions of the cortex while performing a fixed force hand-grip task. Collectively, our results demonstrate the potential of DL frameworks for identifying a more informative feature space in neuroimaging data in a completely data-driven manner, which can in turn yield a better understanding of brain function.

Adult neural stem cell fate is determined by thyroid hormone activation of mitochondrial metabolism

B-12

J.D. Gothié*, A. Sébillot, C. Luongo, K. Le Blay, M. Perret-Jeanneret, S. Remaud, B.A. Demeneix

Maintenance of brain function requires optimal interactions between glial and neuronal populations. In the adult brain, neural stem cells (NSC) located in the subventricular zone (SVZ) produce both neuronal and glial cells. Thyroid hormones (THs) regulate adult NSC differentiation towards a neuronal phenotype, but also have major roles in mitochondrial metabolism. As NSC metabolism relies mainly on glycolysis whereas mature cells preferentially use oxidative phosphorylation, we studied how THs and mitochondrial metabolism interact on NSC fate determination. We showed that a short-term hypothyroidism favored NSCs determination toward a glial rather than a neuronal phenotype in the adult mouse SVZ, whereas culture medium supplemented in THs favored neuronal determination of SVZ-derived NSCs in vitro. Moreover, a transitory hypothyroid period in early remyelination phases following a cuprizone-induced demyelinating insult favors generation of new glial precursors in the SVZ, then enhancing functional recovery of myelinated axons in the corpus callosum. Using a mitochondrial membrane potential marker, we observed greater mitochondrial activity in cells adopting a neuronal phenotype in vivo, and in vitro studies showed that blocking mitochondrial respiration abrogates TH-induced neuronal fate determination. DRP1, a mitochondrial fission mediator, was preferentially activated in cells within the neuronal lineage and was stimulated by THs, showing THs implication in modulating mitochondrial dynamics. Overall, our results show that THs favor adult NSC fate choice toward a neuronal phenotype in the adult SVZ through induction of mitochondrial metabolism. Further research on how metabolic controls contribute to NSC fate decision processes in the adult brain will be critical in the context of neurodegenerative diseases, to understand mechanisms underlying disease susceptibility and progression, and to develop strategies to direct neurogenesis to neuronal or glial cell fates.

Anatomical organization of the mouse subfornical organ

Amirah-Iman Hicks*, Masha Prager-Khoutorsky

B-13

The subfornical organ (SFO) is one of the brain's sensory circumventricular organs (CVOs), which are highly vascularized midline structures lacking a complete blood-brain barrier (BBB). CVOs are characterized by the presence of tanycytes, specialized glia-like cells lining the ventricular floor of the CVOs and interacting with their extensive fenestrated vasculature, thereby contributing to the regulation of the BBB in these areas. Due to the lack of a complete BBB, SFO and other CVOs are unique sites where peripheral circulating factors can penetrate into the central nervous system, influencing neuronal activity and allowing brain cells to monitor blood-borne signals. This provides the brain with information from the periphery and contributes to the generation of centrally-mediated physiological responses to humoral feedback and physiological stressors. Accordingly, SFO plays a key role in the regulation of cardiovascular status, hydromineral balance, energy homeostasis, and metabolism. SFO neurons express a variety of receptors for peripheral signals. Moreover, SFO neurons can be activated by numerous circulating molecules associated with fluid balance (e.g. angiotensin II, sodium, endothelin, vasopressin) and metabolism (e.g. leptin, ghrelin, glucose). While extensive studies have focused on the characterization of the SFO neurons and their roles in the regulation of cardiovascular and metabolic status, the contribution of non-neuronal cells to this regulation is unclear. In this study, we use histological techniques to characterize the spatial outline of the SFO and to examine the location of neurons, as well as non-neuronal cells, including tanycytes, astrocytes, ependymocytes, and endothelial cells within its confines.

The role of diet-induced inflammation during adolescence in the development of obesity and anxiety disorders in adulthood

B-14

Gina Kemp*, David Stellwagen

The "Western Diet," characterized by high levels of saturated fats, refined sugars and red meats, is becoming prevalent globally. A rich literature has linked the consumption of this diet to chronic low-grade inflammation, anxiety and obesity. Yet, the molecular mechanisms that underlie and link these phenotypes are poorly understood. The canonical pro-inflammatory cytokine Tumor Necrosis Factor (TNF) is elevated by high fat diets and has been shown to regulate neuronal AMPA and GABA receptor trafficking. Given this, we hypothesize that diet-induced inflammation mediates long-term changes in appetite and anxiety-related circuitries during a developmental period. To investigate these changes, TNF deficient (TNF KO) mice and their matched controls were put either on regular chow or on high fat (42% kcal from fat) and high sucrose (34% by weight) diet (HFD) from P30 to P60. The mice showed sex and genotype specific differences in food consumption and weight gain profiles. All mice were then put back on regular diet from P60 to P90 and tested for anxiety-like phenotypes. Wild type mice that were previously fed on HFD showed persistent anxiety even after the diet has been switched back to regular chow. However, we do not observe a strong effect in TNF KO mice under the same conditions. This project explores the mechanisms underlying behavioural changes due to "Western Diet" consumption during a developmental period. Understanding the contribution of on-going inflammatory signaling may allow the development of therapies based on FDA-approved drugs, such as Etanercept.

Purkinje cell axonal torpedoes are associated with reduced spike propagation failures and enhanced cerebellar-related behaviour

B-15

Daneck Lang-Ouellette*, Carter Van Eitrem, Pauline de Vanssay de Blavous, Charlotte Rosen, Misha Virdee, and Alanna J. Watt

Focal swellings in the axons of Purkinje cells, or torpedoes, have been frequently observed during disease progression, as well as transiently in the developing cerebellum. Given their prevalence in neurodegenerative diseases, current hypotheses suggest that Purkinje cell axonal torpedoes contribute to pathophysiological axonal function. To elucidate the functional role of Purkinje cell axonal torpedoes in the cerebellum, we used transgenic L7-tau-eGFP mice that brightly label Purkinje cells. Using simultaneous dual recordings from visually-identified Purkinje cells and their axons, we measured the properties of spike propagation with and without the presence of axonal torpedoes. Purkinje cell axons propagate action potentials with high fidelity, with low rates of axonal failures. Surprisingly, we found that Purkinje cell axonal torpedoes displayed even lower axonal failure rates compared to axons without torpedoes. We wondered whether an increase in axonal failure rate led to the formation of axonal torpedoes. Using time-lapse two-photon imaging of live cerebellar slices, we found that Purkinje cell torpedoes were stable over hours, with no new torpedoes formed in ACSF. A non-saturating dose of tetrodotoxin (TTX) caused differential reductions in the firing rate of Purkinje cell somata and axons, thereby mimicking an increase in axon propagation failures. This caused formation of new torpedoes, supporting our hypothesis that torpedoes form when axonal failures are elevated. Finally, we wondered if torpedoes had a functional consequence. To address this, we took advantage of the naturally-occurring variability in motor learning across mice. We found that mice that displayed elevated levels of motor learning had a greater number of Purkinje cell axonal torpedoes, whereas mice that displayed lower levels of motor learning had fewer torpedoes. Taken together, our results suggest that Purkinje cell axons form torpedoes to improve axonal action potential fidelity. The presence of axonal torpedoes is functionally relevant, as they are associated with enhanced cerebellar-related behaviour. These findings argue that rather than reflecting pathophysiology, axonal torpedoes reflect a homeostatic cellular adaptation that preserves axonal function.

A Validation Study for a Virtual Reality Anterior Cervical Discectomy and Fusion (ACDF)

Nicole Ledwos*, Alex Winkler-Schwartz

B-16

BACKGROUND: In the era of evidence based medicine, both neurosurgery and orthopaedic surgery are in need of objective assessment tools for the correct evaluation and teaching of surgical residents. A promising way for medical curricula to achieve both these needs are virtual reality (VR) simulators. The objective of this poster is to present an overview of a novel voxel-based VR simulator and provide a framework for the development of assessment measures for an anterior cervical discectomy and fusion (ACDF) at the C4-C5 level. **METHODS:** In collaboration with OSSimTech, the simulated ACDF scenario will be carried out on the OSSim simulator, a voxel based platform using 3D technology and haptic touch feedback. Consultants, residents and medical students will perform the procedure. Data output for each individual, in the form of a CSV file and a voxel log file, will be used for further analysis. **RESULTS:** The Neurosurgical Simulation Research and Training Centre has previously developed validated objective measures for a brain tumour resection using a finite-element based simulator. Similar expertise will be used to conduct post-hoc analysis aimed at defining metrics for the ACDF. The one-handed, voxel based OSSim simulator provides the opportunity for the exploration of novel objective measures. The developed metrics will fall into the categories of: 1) safety, 2) quality and, 3) efficiency. Subsequently, these metrics may be used to establish proficiency benchmarks that differentiate varying levels of expertise. **CONCLUSION:** The conceptual framework outlined here presents the first attempt at establishing objective assessment measures for an ACDF. It is possible that the developed metrics may provide insight into how varying levels of expertise perform anterior cervical discectomy and fusion procedures and could be a useful tool for the training neurosurgery residents.

Identification of novel cell-surface proteins in axon and glia development in the *Drosophila* visual system

B-17

Zhengya Liu*, Yixu Chen, Yong Rao

Most of our impression of the world is based on sight. Yet the mechanisms that underlie vision are not at all obvious. Normal vision relies on the proper formation of visual circuits during development. The ensheathment of axons by glial processes is essential for visual circuit development. The mechanisms underlying the initial recognition between axon and glia during development, however, remain largely unclear. *Drosophila* has proven to be an excellent model for understanding visual circuit development and function. Our previous study shows that the transmembrane protein Borderless (Bdl) is specifically expressed in wrapping glia (WG) during visual circuit development, and is required for the extension of glial processes and the ensheathment of photoreceptor (R-cell) axons. Bdl functions by interacting with the Ig transmembrane protein Turtle (Tutl) on R-cell axons. However, several key questions remain unanswered. For instance, it remains unknown how the glia-specific expression of Bdl is controlled. That loss of bdl does not completely block glial extension and axon ensheathment indicates the involvements of other unknown cell-surface recognition systems in mediating glial extension and axon ensheathment. We have performed a systematic RNAi genetic screen using UAS-GAL4 system and observed some promising candidate gene as new players in mediating axonal and glial development in the *Drosophila* visual system.

Assessing Signal Quality Assessment of Low Cost EEG Headset Using Functional Connectivity

B-18

Yacine Mahdid*, Stefanie Blain-Moraes

The growth of wearable electroencephalographic (EEG) systems has created unprecedented opportunities to collect neurophysiological data in everyday environments. Assessing the quality of data collected from these systems is paramount both for selecting a wearable EEG system and for interpreting the collected data. We evaluate and compare four wearable EEG systems (the Epoc+, OpenBCI, DSI-24 and Quick-30 Dry EEG) against a research-grade system (Electrical Geodesics Inc) using signal quality, spectral measures and functional connectivity. We demonstrate that functional connectivity metrics provide complementary information to signal quality and spectral measures, and provide a freely available Matlab toolbox containing these measures, which can be effectively used to assess the quality of wearable EEG systems.

How does the brain process sarcastic speech? An ERP investigation

B-19

Maël Mauchand*, Jonathan Caballero, Xiaoming Jiang and Marc D. Pell

Interpreting sarcastic speech requires a listener to retrieve an indirect meaning by recognizing a mismatch between what the speaker says and contextual cues, such as the tone of voice. In this study, we investigated this interpretation process through an event-related potentials (ERP) experiment, with a particular focus on the role of the tone of voice in apprehending sarcastic intent.

Literal and sarcastic stimuli were created by recording verbal compliments (e.g., You are such a great cook) with different tones of voice to suggest a literal interpretation or a sarcastic one. These stimuli were presented to 24 subjects while their brain activity was recorded through EEGs during a friendliness rating task. ERPs were computed for each type of stimulus at the utterance onset, to compare the isolated effects of prosody, and at the onset of the critical word (i.e., great), to investigate the point at which tone of voice allowed listeners to confirm the literal intent of the compliment or its sarcastic interpretation and suggested criticism.

Results show that sarcastic tone of voice is already differentiated from literal speech at sentence onset (as indexed by a reduction of the early P2 component) and is subject to ongoing analysis even before semantic information is fully disclosed (enhanced onset LPC). At the critical word, sarcastic speech surprisingly shows a reduced P600 component, potentially indexing an easier pragmatic integration of the verbal content with the tone of voice compared to literal speech; this might be due to the previous recognition and analysis of the sarcastic tone of voice leading to an anticipated interpretation of the intent.

While more analysis is required to formulate more confident interpretations, these results already argue that the tone of voice plays a significant role at multiple neural processing stages during sarcasm perception, integration and interpretation.

Early elevated tau-PET signal is associated with A β burden, CSF p-tau levels and cognition in cognitively normal, late-middle-aged adults

B-20

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BACKGROUND: Pathological accumulation of tau neurofibrillary tangles in the brain is associated with neurodegeneration and cognitive decline in Alzheimer's disease (AD). Understanding the role of early, pre-symptomatic tau accumulation in preclinical AD is critical for advancing diagnostic and preventive measures, yet its associations with the AD biomarkers amyloid- β (A β), cerebrospinal fluid phosphorylated tau (CSF p-tau), and cognition remain unclear. Using PET imaging, we aimed to investigate these associations in cognitively normal older adults at increased risk of developing AD. **METHODS:** One-hundred-nineteen cognitively normal older adults with a family history of sporadic AD (PREVENT-AD cohort, age=67 \pm 5) underwent tau-PET ([18F]AV-1451), β -amyloid (A β)-PET ([18F]NAV4694) and cognitive assessment. A subsample of 59 participants also had CSF phosphorylated (p)-tau data available. We investigated regional tau SUVR differences between A β -positive and A β -negative individuals using linear regressions. In regions showing significantly higher [18F]AV-1451 binding in A β -positive individuals, we then used linear regressions to assess whether [18F]AV-1451 SUVRs were related to CSF p-tau and cognitive performance. Finally, we repeated the analyses while removing individuals classified as tau-positive (n=7) to assess whether earlier elevations in [18F]AV-1451 signal are relevant to AD-related markers. **RESULTS:** A β -positive individuals had higher [18F]AV-1451 SUVRs than A β -negative ones in predominantly limbic, temporal, occipital, and inferior parietal regions. Increased tau SUVRs in a subset of limbic and temporal regions were also associated with increased CSF p-tau and worse cognitive performance. When focusing only on individuals with subthreshold levels of tau (i.e. those who did not reach the threshold for tau-positivity), these associations remained, except for cognition. **CONCLUSIONS:** Early [18F]AV-1451 binding in AD-typical regions is associated with established AD markers. Except for the association with cognition, these findings were not driven by individuals classified as tau-positive, supporting the idea that very early elevation in tau-related [18F]AV-1451 signal is clinically meaningful.

Visual plasticity induced by short-term monocular deprivation recovers without visual input

B-21

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Short-term molecular deprivation in adults has been shown to temporarily strengthen the contribution of the patched eye to a fused percept. In adults, the effect of monocular deprivation disappears within 30 minutes after the patch has been taken off. Here we investigate whether visual deprivation (sitting in the dark) after patching would preserve the effect of monocular deprivation. We patched six adults with normal vision for two hours with a translucent eye patch. We used a binocular phase combination task to measure each eye's contribution to a fused percept. For the control condition, subjects performed two rounds of baseline tests, were patched for two hours, then performed post-patching measurements at 0, 3, 6, 12, 24, 48, 60 and 96 minutes after patch removal. For the visual deprivation condition, the subjects sat in darkness after patching with both eyes covered for one hour. Subjects then performed the post-patching tests. Each subject completed two sessions for every condition. There was a significant difference (Wilcoxon SignedRank, $P < 0.05$, Cohen's $d = 1.5$) in the effect of monocular deprivation between the darkness and control conditions. Subjects recovered from monocular deprivation even when sitting in the dark. This result suggests that recovery from the patching effect does not require visual input.

Regulation of mitochondrial dynamics in oligodendrocytes by netrin-1

B-22

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Oligodendrocyte mitochondria synthesize ATP and generate carbon chain backbones vital for lipid synthesis and myelin production. The metabolic requirements of the cell are affected by the external environment and exposure to extracellular cues. In response to changing metabolic needs mitochondrial morphology is adjusted through cycles of fusion and fission, known collectively as mitochondrial dynamics. Currently, the mechanisms underlying mitochondrial dynamics in oligodendrocytes remain poorly defined. Here we demonstrate that the extracellular protein netrin-1 signals through Src-family kinase (SFK) activation and ROCK inhibition to regulate mitochondrial dynamics and cellular respiration in oligodendrocytes. Application of netrin-1 induced mitochondrial elongation paired with a reduced rate of oxidative phosphorylation (OXPHOS) and an increase in glycolysis. Inhibition of downstream SFK activity resulted in severe mitochondrial fragmentation and impaired OXPHOS. Conversely, the morphological and metabolic profiles of cells treated with a ROCK inhibitor were similar to netrin-1 treated cells. These netrin-1-dependent morphological changes did not affect levels of mitochondrial fusion or fission proteins (DRP1, MFN2, or OPA1), however, a slight hyperpolarization of the mitochondrial membrane potential was observed suggesting that netrin-1 affects the efficiency of OXPHOS. Collectively, these findings suggest that netrin-1 signalling regulates mitochondrial dynamics in oligodendrocytes and induces a metabolic shift towards glycolysis that may support myelin production through increased lipid synthesis. Current studies aim to determine how mitochondrial form and function are affected by local sources of netrin-1 at the paranodal junction between myelin and the axon.

Auxiliary proteins target distinct regions on AMPARs to modulate receptor function

B-23

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AMPA receptors (AMPARs), a family of ligand gated ion channels, are fundamental for synaptic transmission across all brain regions. Recent work has identified that the AMPAR pore forming subunits co-assemble with a variety of auxiliary proteins. Proteomic analysis suggests that AMPAR signaling complexes are made up of at least 3 families of transmembrane proteins, namely the claudin family of proteins including TARPs and GSG1L, the cornichon homologs (CNIHs) and the CKAMP family. These accessory proteins are garnering much interest as they have been shown to not only regulate the trafficking of receptors into and out of the synapse, but also directly affect their functional behaviour. However, the underlying structural basis for auxiliary protein modulation of AMPARs is poorly characterized. We have identified a hotspot on the AMPAR ligand-binding domain (LBD) that governs auxiliary protein interactions with AMPARs. Our data show that the electropositive KGK motif, a conserved extracellular domain previously identified by our lab, binds exclusively to Type I and Type II TARPs, as well as GSG1L. In contrast, an electronegative region on AMPARs is responsible for CNIH-3 modulation of the receptor. Furthermore, we show that by binding to distinct regions on the receptor, TARPs and CNIHs are able to modulate AMPARs through different gating mechanisms. CKAMP44 is unaffected by mutation of either of these regions, suggesting that this protein exerts its effects via other sites on the channel. In summary, this work establishes that auxiliary proteins modulate AMPARs by targeting distinct structural binding sites, which may be significant for drug development and therapeutics.

Anterolateral tract neurons of the spinal cord develop from the Phox2a lineage

B-24

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Anterolateral tract neurons are found in the dorsal horn of the spinal cord and project to the brain through the anterolateral white matter columns of the spinal cord. These neurons are responsible for transmitting noxious information from the periphery to the brain and thus are a potential therapeutic target in chronic and neuropathic pain disorders. Our experiments show that a developing subpopulation of these neurons expresses the Phox2a transcription factor leading us to create a Phox2a:Cre mouse line. We find that the expression of the TdTomato Cre reporter in Phox2a:Cre; R26-TdTomato+ mice begins at E10, and is highly dynamic until E14 when it takes on a pattern of cell distribution seen in the adult. These TdTomato+ neurons are located in Lamina I, Lamina V and the Lateral Spinal Nucleus. This suggests that superficial dorsal horn projection neurons do not develop by classical dorsal horn lamination mechanisms. Furthermore, using retrograde tracing in adults, we also show that the vast majority of TdTomato+ neurons project through the anterolateral tract. Thus, the Phox2a:Cre transgene is a genetic handle on the mechanism of development of nociceptive projection neurons, and their functional properties such as the transmission of specific nociceptive information.

Exploring neural organization for two different auditory-motor tasks in typical adults and adults who stutter

B-25

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INTRODUCTION: Persistent stuttering is a neurodevelopmental disorder that starts as early as two years of age and continues through adulthood. The potential impact of the disorder on the development of neural networks is unknown, although recent resting state connectivity analyses are consistent with atypical functional organization. The current project is focused on examining the impact of the disorder on the neural organization of sensorimotor networks for speech and nonspeech. We examined the behavior and brain contributions of individuals who stutter (IWS) to two auditory-motor tasks, vowel production and paced tapping. We examined the task positive and task negative networks for each behavior and evaluated the independent components that comprise each. **METHODS:** For the speech task, participants produced the vowel /a/ while hearing their own voice in real time through headphones. On some trials, the pitch of the feedback was shifted, eliciting a compensatory response. For the tapping task, participants listened to a metronome stimulus and kept time by squeezing a pressure pad between their fingers. The metronome stimulus contained sudden increases or decreases in tempo, and the participant had to adjust their production to the change. Both tasks were completed inside and outside of an MRI scanner. In addition to a univariate general linear modeling (GLM) approach to examine both task positive and task negative differences in the groups, we used independent component analysis (ICA) to extract information from the data not apparent from GLM results. **RESULTS:** The behavioral performance for both tasks was comparable across the groups. Differences in performance were primarily related to increased timing variability in the stuttering group. Neural activation and deactivation and the composition of the independent positive and negative components differed in a number of ways. For the speech task, IWS had, atypical deactivation in middle temporal and superior frontal areas. For tapping, similar neural patterns were observed in auditory-motor integration areas. Differences in the independent components were observed, reflecting an atypical neural organization for the IWS with different patterns of correlated-anti-correlated activity within components. **CONCLUSION:** While the sensorimotor behavior of IWS is only mildly impacted by the disorder, functional neural organization is substantially affected, likely reflecting compensatory development. These differences were observed in speech and nonspeech behavior, possibly due to a common impact on sensorimotor timing. The atypical neural organization, including differences in distribution and balance of task activation and deactivation, highlight an importance consequence of neurodevelopmental problems with substantial implications for treatment.

The pulsatile rhythm of circulating growth hormone might be governed by the dopaminergic ultradian oscillator

B-26

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Growth hormone (GH) is synthesized in the somatotrophs of the anterior pituitary gland in all vertebrates. It regulates growth and metabolism via multiple tissue/cell type targets and circulating GH has been frequently reported to exhibit a pulsatile rhythm of around 3-hrs. GH secretion is stimulated by growth hormone releasing hormone (GHRH) and inhibited by somatostatin, two hypothalamic peptide that are released into the median eminence and reach the pituitary gland via the portal vessels. Several studies indicate that also dopamine (DA) inhibits GH release, possibly through down regulation of GHRH, and that dopamine receptors D1 and/or D2 are involved in this process. However, a role of DA specifically in the temporal regulation of GH release has not yet been explored. We hypothesized that a recently discovered dopaminergic ultradian oscillator, which produces behavioral rhythms with a period of 3-5 hours, might be regulating the pulsatile rhythm of circulating GH. We previously reported that the activation of the midbrain VTA dopaminergic neurons lengthened the period of the oscillator. We now show that selective, genetically mediated ablation of VTA DA neurons result in a shortening of the GH inter-pulse interval from 3-4hrs to ~1hr. This data indicates that the VTA dopaminergic ultradian oscillator may rhythmically gate the release of GH.

Bioinformatic analysis of mouse PFC DNA methylation in response to acute, sub-chronic and chronic neuropathic pain

B-27

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AIM OF INVESTIGATION:

Chronic pain is associated with the functional and anatomical remodeling of prefrontal cortex (PFC) in both human patients and rodent models. The PFC is commonly implicated in pain modulation and pain-related comorbidities. Following therapeutic intervention, these changes can be partially reversed. Understanding the mechanisms underlying recovery of cortical function may provide insights into chronic pain's pathobiology and reveal new treatment approaches. As a reversible regulator of gene expression that is responsive to environmental effects, DNA methylation is an ideal candidate mechanism to mediate PFC plasticity in response to chronic pain. We have previously shown PFC DNA methylation undergoes significant changes 6 months post-spared nerve injury (SNI) and results in the differential methylation of thousands of PFC genes. The current study used epigenome-wide methylation analysis to track changes in the PFC post-SNI at acute, sub-chronic and chronic time points and to identify pain-related genes and functional pathways over time. We hypothesize that DNA methylation contributes to the development and maintenance of chronic pain over time by mediating changes in PFC gene expression. METHODS: Male six week old CD-1 mice underwent SNI or sham surgery and PFC was harvested from Sham or SNI at 2-days, 2-weeks or 6-months post-injury. DNA was bisulfite-converted and sequence-capture acquired genes for Illumina sequencing to determine DNA methylation levels. Bioinformatic analyses determined differential methylation and functional pathway analysis was performed to identify pain-relevant genes related to chronic pain development and maintenance. RESULTS: DNA methylation changes were observed in hundreds of genes, comparing SNI and sham animals at acute, sub-chronic and chronic time points. Examples include differential methylation of methyl-CpG binding domain protein 4 (Mbd4) in 6-month post-SNI versus 6-month sham animals. The chronic time point has the greatest number of differentially methylated genes. DISCUSSION/CONCLUSIONS: Identifying pathways unique to time point or injury condition may reveal specific mechanisms regulating chronic pain's development and maintenance over time, allowing for a better understanding of the overall response to chronic pain. Determining the key regulatory pathways or epigenetic mechanisms underlying chronic pain may provide novel intervention targets or therapies that better account for the complex nature of chronic pain.

Regulation of Retinal Polarity by the Endocytic Adaptor Protein Numb through the Crb1 Complex

B-28

Maude Vinette*, Marie-Claude Bélanger, Christine Jolicoeur, Mina Gabraie, Pierre Lachapelle, Michel Cayouette

The loss of cell polarity plays a key part in retinal dystrophies such as retinitis pigmentosa (RP) and Leber congenital amaurosis (LCA), resulting in photoreceptor (PR) degeneration and vision loss. Many disease-causing mutations in the polarity determinant Crumbs Homologue 1 (Crb1) have been identified, resulting in the loss of apical adhesions between PR and Müller cells leading to degeneration. Although the role of Crb1 is well established, little is known about how it is regulated. A novel interacting partner for Crb1, Numb, has been identified and further demonstrated to affect the levels of Crb1 when deleted in Müller glia. Here, we therefore discuss the potential mechanism behind which Numb regulates Crb1 homeostasis to maintain retinal architecture and photoreceptor integrity.

The influence of developmental and social experience on plasticity in the auditory system of female Zebra Finches

Erin Wall*; Sarah Woolley

B-29

Vocal communication requires the brain to attend to, learn, and remember complex information in the environment. All species that learn vocal communication depend on the brain's ability to develop auditory filters that extract salient sounds from noise. Communication is a critical component of social behavior, yet we have limited understanding of how social interactions shape the perception of vocal signals. In songbirds, males produce learned vocal signals ('songs') that females use to assess identity and mate quality. While female zebra finches do not sing, they rely on early exposure to song to properly interpret these communication signals. However, the types of experiences necessary to shape the neural mechanisms involved in signal discrimination and mate choice remain unclear. To address this open question, I investigate the experiences important for female songbirds to extract information from vocal signals, and the effects these experiences have on neural plasticity and preference. Previous research indicates that female zebra finches develop a strong preference for their mate's song that may be mediated by the quality of social interactions and pair bonding. The emergence of this preference indicates that particular social experiences lead to neural plasticity that alters neural responses to the mate's song. While normally-reared females are capable of properly encoding these signals, it is unclear how developmental experience with song affects adult preference formation. To answer this, I expose females, both normally-reared and song-naïve, to a male at different levels of social interaction (co-habitation or auditory interactions). I found that both song-naïve and normally-reared females developed a preference for a male's song when allowed to cohabitate and pair bond. Females that only heard this male's song did not prefer his song, suggesting the physical or visual stimuli involved in pair bonding behavior play an important role. These social experiences may promote neural plasticity sufficient to drive auditory preference formation even in females reared without song exposure during development.

Oscillations and neuronal network synchronization in in vitro brain preparations and in an animal model of mesial temporal lobe epilepsy

B-30

Siyan Wang*, Li-Yuan Chen, Maxime Lévesque and Massimo Avoli

Neuronal synchronization represents the integrated activity occurring overtime among neuronal networks that are located in one or more interconnected brain structures. Under normal conditions, neuronal synchronization makes the brain generate specific EEG rhythms that are associated with different physiological states extending from cognitive functions to specific sleep states. However, excessive and thus abnormal neuronal synchronization can cause the occurrence of both focal and generalized epileptic discharges. In our laboratory, we aim to better understand the cellular mechanisms of pathological network synchronization that leads to epileptiform discharges. More specifically, we analyse single-unit activity during epileptiform activities recorded in vitro. Using the pilocarpine model of mesial temporal lobe epilepsy, we also study in vivo the relationship between high-frequency oscillations (ripples: 80-200 Hz and fast ripples: 250-500 Hz), epileptogenesis and ictogenesis. Finally, we apply optogenetic stimulation techniques to better understand the specific contribution of interneurons and principal cells to epileptiform activities recorded in the temporal lobe of epileptic animals.

The role of mTORC2 in the development of chronic pain

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B-31

Neuropathic pain is a form of chronic pain that can persist for years as a result of nerve injury. Inflammatory pain is another form of pain that is commonly acute, and involves tissue damage due to inflammation. Changes associated with the development of inflammatory and neuropathic pain involve the reorganization of pain circuitry, and alterations in the gene expression. mTOR is a highly evolutionarily conserved serine/threonine kinase that regulates cell homeostasis through key cellular processes, including cell growth and proliferation, translation, autophagy, and cytoskeleton organization. mTOR is present in two structurally and functionally distinct multiprotein complexes: mTORC1 (mTOR Complex 1) and mTORC2. The activity of mTORC1 is required for the development of chronic pain, mainly via regulation of mRNA translation. Much less is known about mTORC2, which has recently emerged as a key signaling molecule in the variety of cellular processes. To study the role of mTORC2 in pain, we selectively ablated rictor, a key protein within the mTORC2, in Nav1.8-positive nociceptors. Our behavioural experiments demonstrate that rictor conditional KO (cKO) mice exhibit reduced hypersensitivity in a mouse model of inflammatory pain, complete-freund's adjuvant (CFA), but not in the model of neuropathic pain, spared-nerve injury (SNI). To ensure that behavioural effects are not a result of developmental changes from the conditional knockout of Rictor, immunohistochemistry and western blot analysis were carried out. We also performed experiments to study the effect of rictor cKO on intracellular signaling following inflammation and tissue injury. In summary, our study demonstrates for the first time the central role of mTORC2 in nociceptors in the development of pain hypersensitivity in response to inflammation.

Hippocampal inputs to the nucleus accumbens promote consumptive pleasure

B-32

Angela Yang*, Jesse Mendoza, Christopher Lafferty, Jonathan Britt

Anhedonia, the inability to experience pleasure, is a prevalent symptom in many psychiatric disorders such as depression and schizophrenia. The nucleus accumbens (NAc) has been implicated in the sensation of pleasure in both human fMRI and rodent pharmacology studies. In rats, mu-opioid receptor agonists targeted to the rostral NAc shell increase consumptive pleasure, however the physiological underpinnings of this phenomenon are poorly delineated. Mu-opioid receptor stimulation alters NAc physiology in a variety of ways, including by reducing glutamate input in a pathway-specific manner. To determine the extent to which specific glutamate afferents can influence consumptive pleasure, we employed optogenetic tools in mice to manipulate input activity in the NAc from the ventral hippocampus, basolateral amygdala, and midline thalamus. We used licks per bout as an objective measure of pleasure, which is the average number of licks in each bout of liquid sucrose consumption. We report that high-frequency stimulation (16-48Hz) of any glutamatergic input to the NAc terminates feeding, whereas 1Hz stimulation specifically of hippocampal inputs significantly increases licks per bout. Inhibition of dopamine D1 receptor-containing (D1R+) medium spiny neurons (MSNs) in the NAc also enhances licks per bout. It is possible that low frequency stimulation of hippocampal inputs promotes mu-opioid signaling through a complex balance of activity in D1R+ MSNs. Current experiments aim to further characterize this phenomenon with the hope that a better understanding of NAc-generated pleasure will help guide treatment development efforts for pathologies involving anhedonia.

Heterogeneous contributions of the medial septum in the hippocampal code for time

B-33

H. Yong*, M. P. Brandon

Recent work has shown that hippocampal neurons code for the time spent in the delay period on a delayed spatial alternation task. These "time cells" have been shown to require input from the medial septum (MS) as muscimol inactivation of the MS disrupted the activity of time cells and impaired memory. However, the exact role of the MS in time cell function remains unclear as the inactivation persisted for the full duration of the behavior task. It is possible that time cells may require information computed outside of a delay zone by other areas that rely on the MS. Also, the inactivation silences the activity of all septal neurons, thus it is unclear which cell populations within the MS support the time cell activity. We, therefore, pursued an optogenetic approach to selectively silence genetically defined cell populations within the MS only when animals ran on the treadmill in the delayed spatial alternation task. Here, we specifically tested the role of GABAergic neurons in the MS, which are believed to have a role in the generation of the hippocampal theta rhythm. We injected the VGAT::Cre animals with AAVDJ-EF1a-Flex-ArchT-eGFP. They were trained to alternate in the T-maze, and to run on the treadmill for 10s between each alternation. Activity of time cells was recorded from CA1 region of the hippocampus, and the MS was silenced when animals ran on the treadmill. We found that optogenetic inactivation of the septal GABAergic neurons cause a 70-80% reduction in theta power, similar to results observed with the muscimol inactivation. Also, the optogenetic inactivation had heterogeneous effects on the activity of time cells. However, their memory performance remained intact. Next, we plan to assess the role of the remaining cell types in the MS including cholinergic and glutamatergic neurons. Together, this data will reveal which MS populations are important for time cell function, and this will shed light on the underlying mechanisms of these time cells.

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