ABSTRACT BOOKLET

STUDENT POSTERS

2019 IPN RETREAT

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1-A “Mental Workload Estimation Using Wireless EEG Signals”

Quadri Adewale, George Panoutsos

Previous studies have shown that electroencephalogram (EEG) can be used in estimating mental workload. However, developing fast and reliable models for cross-task, cross-subject and cross-session classifications of workload remains a challenge. In this study, a wireless Emotiv EPOC headset was used to evaluate workload in two different mental tasks: n-back task and mental arithmetic task. 0-back task and 2-back task were employed as low and high workload in the n-back task while 1-digit and 3-digit addition were used as the two different workload levels in the arithmetic task. Using power spectral density as features, a fast signal processing and feature extraction framework was developed to facilitate real-time estimation of workload. Within-session accuracies of 98.5% and 95.5% were achieved in the n-back and arithmetic tasks respectively. Adaptive subspace feature matching (ASFM) was applied for cross-session, cross-task and cross-subject classifications. The feature adaptation provided average cross-session accuracies of 80.5% and 74.4% in the n-back and the arithmetic tasks respectively. An average cross-task accuracy of 68.6% was achieved while cross-subject accuracies were 74.4% and 64.1% in the n-back and arithmetic tasks respectively. The framework generalized well across subjects and tasks, and it provided a promising approach towards developing subject and task-independent models. This study also shows that a consumer-level wireless EEG headset can be applied in cognitive monitoring for real-time estimation of workload in practice.

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1-B "Understanding the limits of amblyopic stereopsis"

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Amblyopia (lazy eye) develops due to an impaired monocular input during childhood. The loss of visual acuity in the affected eye has debilitating consequences for the ability to perceive depth from stereopsis (comparing inputs from the two eyes). Improvement in stereopsis (stereo) post treatment is difficult to measure as common clinical stereo tests are often heavily quantized and unable to detect residual stereoacuity in amblyopic patients. The lack of accurate baseline stereoacuity scores limits its use as a diagnostic measure and hinders our understanding of reduced amblyopic binocularity. This study employs a new a random dot stereogram test able to quantify previously immeasurable amblyopic stereoacuity. Participants wear 3D glasses and require stereo to identify the location of a target in-depth on a screen. Further, we apply the equivalent noise method to measure an individual's equivalent internal noise (signal to noise ratio of disparity signals) and processing efficiency (how efficiently the system processes noisy input). The second aim of the study is to determine the role of these two factors in reduced amblyopic stereo. The study is still in progress. We have tested 29 amblyopic (7 strabismic, 13 males) and 14 control (5 males) adults. 62% of amblyopic subjects are considered "stereoblind" when tested with the clinical Randot Preschool test, compared to only 41% with our test. Of those able to complete our task, the mean amblyopic stereoacuity is 164 arcsec (SD = 4.24), a factor of 2.65 higher than that of controls (M = 61.8 arcsec, SD = 1.71). We predict the comparison in equivalent internal noise and processing efficiency between amblyopic subjects and controls may explain deficits in amblyopic stereo. Thus far, the study presents a more sensitive test for measuring stereo in amblyopia. This will lead to better understanding of the underlying causes of diminished amblyopic stereo and improved treatments.

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1-C "Perineuronal nets in the ventromedial prefrontal cortex of depressed suicides with a history of child abuse"

Belliveau, C.[1,2], Tanti, A.[2], McFarquhar, A.[2], Denux, F.[2,] Davoli, M.A.[2], Mechawar, N.[1,2,3]

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Background: Experiencing child abuse (CA), defined as physical, emotional and/or sexual maltreatment or neglect, is considered as one of the strongest predictors of major depressive disorder and suicide later in life. Although CA has been associated with functional changes in cortical areas involved in mood regulation, little is currently known about its effects on the brain at a cellular level. Childhood and adolescence are characterized by critical periods of heightened plasticity, in which neural circuits can be more easily modified. The closure of these critical periods is thought to be driven by the development of perineuronal nets (PNNs) around parvalbumin-positive inhibitory interneurons (PV). We hypothesize that child abuse occurring during these critical periods long-lastingly alters cortical connectivity in areas involved in emotion by disrupting the normal recruitment of PNNs.

Methods: Post-mortem human hippocampal, entorhinal cortex, subiculum and ventromedial prefrontal cortex (vmPFC) samples (Douglas-Bell Canada Brain Bank) were immunolabeled for PV and NeuN. PNNs were visualized using biotin-conjugated Westeria Floribunda Lectin followed by immunofluorescent detection using fluorophore-conjugated streptavidin. Whole slide images were analyzed using QuPath to compare distribution of PNNs between psychiatrically healthy controls and depressed suicides with or without a history of CA.

Results: CA was found to be associated with higher densities of PNNs in the vmPFC of depressed suicides, specifically in layers III, IV & V. Preliminary results show that this altered recruitment of PNNs may be vmPFC specific.

Conclusions: This work, the first to describe the distribution of PNNs in the brain of depressed suicides, reveals a lasting impact of CA on PNNs in the vmPFC. This may represent a mechanism through which early-life adversity increases vulnerability to psychopathologies and suicide.

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1-D "Dual modulation of mGlu2 and 5-HT2A receptors as a novel approach to alleviate L-DOPA-induced dyskinesia"

Bourgeois-Cayer E[1,2], Belliveau S[1,2], Frouni I[1,3], Kwan C[1,2], Bédard D[1], Hamadjida A[1,2], Huot P.[1,2,3,4,5]

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Introduction: L-3,4-dihydroxyphenylalanine (L-DOPA) remains the most effective treatment for Parkinson's disease (PD). However, chronic administration of L-DOPA leads to the emergence of motor complications such as dyskinesia in the vast majority of patients. Serotonin 2A ($5\text{-}HT_{2A}$) receptor blockade is a validated approach to alleviate dyskinesia, but its effectiveness appears to be of limited magnitude. Recently, we have demonstrated that activation of metabotropic glutamate 2 ($mGlu_2$) receptors reduces dyskinesia in the 6-hydroxydopamine (6-OHDA)-lesioned rat. Based on the fact that $5\text{-}HT_{2A}$ and $mGlu_2$ receptors form a functional hetero-complex, we hypothesised that combining EMD-281,014, the most selective $5\text{-}HT_{2A}$ antagonist commercially-available with LY-354,740, a selective $mGlu_2$ orthosteric agonist (OA) and LY-487,379, the most selective $mGlu_2$ positive allosteric modulator (PAM) commercially-available, would be more effective at enhancing L-DOPA anti-parkinsonian action and at alleviating dyskinesia than modulating $5\text{-}HT_{2A}$ and $mGlu_2$ receptors separately.

Methods: Rats were rendered hemi-parkinsonian by stereotaxic injection of 6-OHDA into the right medial forebrain bundle. Following a recovery period, degree of parkinsonism was assessed using the cylinder test. Rats were then primed with daily administration of L-DOPA to induce stable axial, limb and oro-lingual (ALO) abnormal involuntary movements (AIMs). On experimental days, rats were administered L-DOPA in combination with previously determined effective doses of each of EMD-281,014 (vehicle, 0.03 and 0.1 mg/kg s.c), LY-354,740 (vehicle and 0.1 mg/kg s.c.), and LY-487,379 (vehicle and 0.1 mg/kg s.c.) after which ALO AIMs were assessed for 2 min, every 20 min, for 180 min. After a 3-day washout period, an acute low-dose of L-DOPA was administered with a combination of EMD-281,014/LY-354,740/LY-487,379, and the effect on L-DOPA anti-parkinsonian action was determined by the cylinder test.

Results: Combining EMD-281,014 (0.03 mg/kg) with either LY-487,379 (0.1mg/kg) or LY-354,740 (0.1mg/kg) leads to significant reduction of right

forepaw use by 66% and 76% respectively and combining EMD-281,014 (0.1 mg/kg) with LY-354,740 (0.1 mg/kg) led to a 44% reduction compared to L-DOPA alone. Combining EMD-281,014 (0.1mg/kg) with LY-487,379 significantly reduced ALO AIMs duration by 10% ($P < 0.05$), when compared to vehicle. Importantly, combining EMD-281,014 with LY-354,740 and LY-487,379 did not interfere with L-DOPA anti-parkinsonian action.

Conclusions: Our results suggest that there may be synergistic anti-parkinsonian benefit achieved when combining 5-HT_{2A} blockade and $mGlu_2$ activation in the 6-OHDA-lesioned rat model of PD with either a PAM or an OA but not both. Additionally, optimal synergistic anti-dyskinetic benefit in this study was achieved when combining EMD-281,014 and LY-487,379.

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2-A "The developmental connectome of intrinsically photosensitive retinal ganglion cells (ipRGCs)"

Thomas Brown, Adele Tufford and Michel Cayouette

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 to the pupillary light reflex. In adults, their connectivity patterns and 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 two postnatal weeks 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 ipRGC send their axons, or the retina, where ipRGC cell bodies are located. Injections will be done at three developmental time-points (P1, P4, and P6) 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. After performing viral injections in SCN of OPN4-Cre:ROSA-TVA-G mice at postnatal days 1 and 4, we have observed a large number of Müller glia and non-photosensitive RGCs labelled with GFP, suggesting connections between ipRGCs and these cell types occur at this stage. Further investigations will characterize the full repertoire of ipRGC-connecting cell types in the retina during postnatal development, as well as determine the role of these connections.

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2-B "The evolution of the hippocampus subfields volume across lifespan in healthy aging"

Aurélie Bussy[1,2], Eric Plitman[2,3], Alyssa Salaciak[2], Sarah Farzin[2], Saashi A. Bedford[1,2], Stephanie Tullo[1,2], Marie-Lise Beland[2], Gabriel A. Devenyi[2,3], M. Mallar Chakravarty[1,2,3,4]

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Introduction: The hippocampus plays an important role in memory consolidation and spatial memory. Healthy aging (HA) is associated with a gradual decline in memory and shrinkage of hippocampal volume. The hippocampus is also one of the major areas wherein Alzheimer's Disease (AD) pathologies are identified. Importantly, the progressive degeneration of the hippocampus and its subfields across the adult lifespan is presently not well characterized. The goal of the present work is to evaluate and identify volumetric modifications in hippocampal subfields during HA.

Methods: The present work included 180 healthy participants (ages 18-80) to investigate lifespan changes in hippocampus volume during HA. The volume of the hippocampus and its subfields (Cornus Ammonis (CA)1, CA2CA3, CA4 and dentate gyrus (CA4DG), stratum radiatum/lacunosum/moleculare, subiculum, fimbria, fornix, alveus and mammillary bodies) were estimated using T1-weighted images (1mm3 voxels) and the MAGeT Brain algorithm. Analyses were carried out using general linear models. Akaike information criterion was used to compare models and select the most probable age relationships from multiple fits (e.g. linear, quadratic, and cubic) for each structure of interest. A Bonferroni correction have been used for multiple comparisons correction, at a $p < 0.05$ threshold for significance. Analyses included sex, MMSE score, years of education, and APOE4 status as covariates.

Results: Total hippocampus showed an interaction between cubic age and sex. Including total hippocampal volume as a covariate, the right CA1 and the right alveus were positively cubically related to age ($p=0.008$ and $p<0.001$, respectively), and the right and left CA4DG were negatively linearly related to age ($p=0.04$ and $p=0.001$, respectively).

Conclusion: Specific subfields of the hippocampus are more (e.g. CA1, alveus) or less (e.g. CA4DG) preserved in HA. Future aims for this study include extending analyses to additionally include patients with mild cognitive impairment and AD.

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2-C "Effects of KCC2 antagonism on ictogenesis and neuronal excitability in the entorhinal cortex *in vitro*"

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Mesial temporal lobe epilepsy (MTLE) is a chronic condition that involves focal seizures initiated from limbic areas such as the hippocampus and entorhinal cortex (EC). With up to one-third of patients not achieving effective seizure control, it is one of the most refractory forms of epilepsy that requires research effort in developing more effective therapeutic strategies. A known player in seizure initiation – ictogenesis – is the potassium-chloride cotransporter 2 (KCC2). Previous experiments have shown that antagonizing KCC2 activity stops seizure generation and increases the occurrence of interictal events but the exact mechanism involved in these changes remain elusive. Using the *in vitro* 4-aminopyridine (4AP) model of epileptiform synchronization in the rat EC, we studied the effects of the KCC2 antagonist VU0463271 on neuronal activity during seizures and interictal events recorded using tetrodes. We found that 4AP-induced seizures – associated with significant increases in interneurons and principal cells activities – were transformed into shorter events that were not accompanied by significant increases in interneuron or principal cell firing. Additionally, interictal events that persisted at an accelerated frequency of occurrence during VU0463271 application were associated with significant increases in interneuron and principal cell activity. Further analysis revealed that the interneuron and principal cell firing rate increases during interictal events were greater under VU0463271 application without changes to underlying neuronal synchronicity. Overall, our results demonstrate that KCC2 antagonism in the EC impedes ictogenesis despite enhancing neuronal excitability.

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2-D "Neuroprotective effects of hypothermia in neonatal arterial ischemic stroke"

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Background: No targeted treatments are currently available for the management of neonatal arterial ischemic stroke (NAIS). Epidemiological studies of NAIS showed that perinatal infection/inflammation, *peripartum* hypoxia, and occlusion of the internal carotid tree are the main determinants of NAIS. The well-established benefit of therapeutic hypothermia (HT) in neonatal encephalopathy due to diffuse hypoxia-ischemia provides a rational for the potential use of HT as a neuroprotective strategy in NAIS.

Methods: We used our triple-hit rat model at postnatal day 12 (perinatal inflammation, hypoxia, and carotid occlusion) to reproduce the most prevalent human physiopathological scenario in NAIS. Briefly, inflammation was induced by injecting intraperitoneally (ip) 50 µg/kg of lipopolysaccharide from *E.coli*. Four hours later, the right common carotid artery was ligated, then hypoxia was induced (8% O2, 1 h 30 min). Pups were submitted (or not) to HT (32.5 ± 0.4°C, 4 h). Control pups received a saline injection followed by a sham surgery and without hypoxia and HT. The volume of stroke on magnetic resonance imaging (MRI), the [18F] FDG metabolic activity by positron emission tomography / computed tomography (PET/CT), and the motor behavior were used to measure the neuroprotective effect of HT.

Results: HT had neuroprotective effects by: (*i*) preventing the occurrence of 44% of stroke cases, (*ii*) reducing by 37% the volume of strokes, (*iii*) enhancing [18F] FDG metabolic activity within the territory of the occluded carotid artery, and (*iv*) improving the motor behavior. Interestingly, morphometric and metabolic techniques showed that HT provide a consistent neuroprotective effect located in the motor cortex, hippocampus, and caudate putamen.

Conclusions: These results are highly relevant and potentially translational to human NAIS in which the most prominent sequelae affect the motor system. Our study combining anatomical and metabolic imaging and behavioral studies provides compelling evidence of the neuroprotective effect of HT in NAIS. These findings would hopefully pave new grounds for the use of HT in improving outcomes of NAIS.

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3-A "Calcium dynamics and spike-timing-dependent plasticity in basket cell dendrites"

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Basket cells (BCs) are fast-spiking, non-accommodating inhibitory interneurons which make up approximately 32% of GABAergic neurons in the visual cortex. In the primary visual cortex, fast-spiking interneurons have been shown to exhibit ocular dominance plasticity distinct from pyramidal cells (PCs) following monocular deprivation. Thus, understanding the rules and mechanisms of interneuron plasticity can provide important insights into the development of healthy cortical circuits. Postsynaptic calcium dynamics facilitate site-specific synaptic plasticity, for example, by signaling coincident pre- and postsynaptic activation. However, the mechanism and role of calcium dynamics at excitatory synapses onto interneurons are poorly understood. Previous studies done in the hippocampus suggest that excitatory synapses onto interneurons exhibit non-Hebbian plasticity, in which coincident firing of pre- and postsynaptic neurons paradoxically results in long-term depression (LTD). This phenomenon was dependent on non-linear summation of calcium transients facilitated by calcium-permeable AMPA receptors.

Here, we described characteristics of PC-BC synapses in the visual cortex, such as the location of synaptic contacts and action potential backpropagation in BC dendrites. In agreement with results from the hippocampus, we observed non-Hebbian plasticity at PC-BC synapses, where both pre-before-post and post-before-pre stimulation lead to LTD. We also found that varying the timing of synaptic stimulation and somatic action potentials induced different calcium non-linearities, where pre-before-post stimulation lead to supralinear calcium transients and post-before-pre lead to sublinear. Our preliminary results show correlation between spike-timings and calcium non-linearities in PC-BC synapses. We are currently exploring whether or not the calcium non-linearities in BC dendrites are correlated with plasticity in the visual cortex.

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3-B "Localization of Schizophrenia-Associated Protein Dysbindin-1 within the Suprachiasmatic Nucleus"

Marie-Ève Cloutier, Tara Delorme, Nicola Ludin, Jane Zhu, Lalit Srivastava, Nicolas Cermakian

Cognitive deficits are considered a core symptom of schizophrenia. Mice with a loss-of-function mutation in Dysbindin-1 gene, a risk factor for schizophrenia, exhibit behavioral and cognitive deficits described in patients. As we have previously reported, circadian disruptions can worsen these deficits. Broadly, our aim is to localize Dysbindin-1 protein, involved in intracellular trafficking and synaptic transmission, in the suprachiasmatic nucleus (SCN), the site of the central clock in mammals, to examine Dysbindin-1 role in the SCN neuron function. This will be done by immunostaining for Dysbindin-1 protein, vasoactive intestinal peptide (VIP), a marker for SCN core, and arginine vasopressin (AVP), a marker for SCN shell. We first developed an immunohistochemistry (IHC) protocol to stain for AVP and VIP neurons by optimizing incubation times and antibody concentrations. Mice were perfused and IHC was performed on 30 µm brain sections using anti-AVP and anti-VIP antibodies. We found that both neuron groups were best visualized when blocked with donkey normal serum and stained for 48h at 4°C with primary antibody (1:1000). We are presently working on protocols to stain for Dysbindin-1 and to improve VIP staining in the SCN. This work will help understanding the molecular and cellular mechanisms for the interaction between schizophrenia and circadian disruptions.

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3-C "Using transcriptome data acquired through single-cell RNA sequencing to characterize glial subtypes in Drosophila"

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Glial cells in the central nervous system are essential for neural development, ion homeostasis, neuronal metabolism and excitability, as well as behavior, but the molecular and cellular mechanisms underlying these effects are incompletely understood. We aim to clarify the diversity of glial subtypes in the Drosophila brain and ventral nerve cord at the level of the transcriptome, using both published and unpublished single-cell RNA sequencing datasets acquired with the 10x Chromium microfluidics system. By providing a clearer understanding of the gene expression signatures of distinct glial cell types we hope to illuminate molecular mechanisms of how glia influence brain development and function.

Taking advantage of RStudio's graphic interface to perform cluster analysis of larval and adult central nervous systems, we have successfully identified most glial cell types in larvae using known combinations of markers. We are currently working to identify common and distinct molecular signatures between adults and larvae, with particular focus on astrocytes and ensheathing glia, which are both located near synapses. Ultimately, this research will increase the breadth of understanding of glial cells and will identify new candidate genes and pathways to understand how these distinct glial subtypes contribute to the proper function and development of the central nervous system.

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3-D "CNS-derived exosomes carry heme oxygenase-1 in peripheral biofluids of mice and humans"

Marisa Cressatti, Julia Galindez, Ana M. Velly, Mervyn Gornitsky, Hyman M. Schipper

Background: Numerous pathological features of primary neurodegenerative disorders are manifest in peripheral tissues. Heme oxygenase-1 (HO-1), a highly inducible stress protein that degrades heme to biliverdin, carbon monoxide and free ferrous iron, is augmented in brain (substantia nigra) astrocytes and saliva of patients with idiopathic Parkinson disease (PD). We recently demonstrated that microRNA (miR)-153 and miR-223, which target α-synuclein (a key pathogenic protein in PD-affected tissues), are significantly downregulated in brain and serum of parkinsonian GFAP.HMOX1 mice and in saliva of human PD subjects. Exosomes are generated within late endosomal compartments and secreted when these compartments fuse with the plasma membrane, thereby transporting miRNA, mRNA and protein cargo from cell-to-cell.

Hypothesis: Exosomal transport of HO-1 from brain to periphery may be responsible for some of the systemic manifestations observed in human and experimental parkinsonism.

Methods: GLAST-positive (astrocyte-derived) and L1CAM-positive (neuron-derived) exosomes were purified from mouse and human biofluids using immune-affinity capture. HO-1 was assayed in all fractions using Western blot and ELISA.

Results: In 6-month old GFAP.HMOX1 transgenic mice (selectively overexpressing human HO-1 in astrocytes), serum exosomes contained increased HO-1 levels compared to age-matched, wild-type controls. Most of the serum exosomal HO-1 in the mice was localized to L1CAM (neuronal-derived) exosomes, indicative of its neural origin. Similarly, HO- 1 was detected, for the first time, in total (Alix- and TSG101-positive), L1CAM-positive and GLAST-positive exosomal fractions of healthy human saliva and other biofluids. HO-1 levels in exosome-free fractions of both mouse and human biofluids were minimal relative to exosomal HO-1 content, suggesting circulating HO-1 is primarily carried in exosomes.

Conclusions: Our findings lend support to the hypothesis that exosomal transport of HO-1 and other cargo from brain to periphery may be responsible for some of the systemic pathology observed in PD and other primary neurodegenerative disorders.

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4-A "Identifying individuals from resting-state MEG"

Jason Da Silva Castanheira[1], Hector Orozco Perez[1], Bratislav Mišić[2], Sylvain Baillet[2]

[1]These authors contributed equally to this work
[2]These authors contributed equally to this work

Neuroscience often collapses heterogeneity among individuals; however, previous efforts show that there is considerable variability among the anatomical and functional organization of human brains, and that these differences are both reliable and meaningful. For instance, resting-state fMRI can successfully identify individuals from their functional connectome. Yet, the majority of work on neural fingerprinting to date is restricted to fMRI, with a short duration between scans. The present study extends this line of work to resting-state oscillatory dynamics. We used 158 MEG scans from the Open MEG Archive (OMEGA) database to derive two novel neural fingerprinting methods based on ongoing MEG resting-state activity, extracting power spectrum density (PSD) profiles and resting-state functional connectomes. The identification of individuals was successful using both the functional connectome and PSD profile approaches (accuracy > 90%). Activity in the beta band (13-30 Hz) and occipital regions are distinguished as the most characteristic features differentiating individuals. In addition, we assess the quantity of data required to identify individuals: functional connectome fingerprinting remains successful even with short segments of data (i.e. 30 seconds), while the PSD profile method decreases in performance (<90% accuracy). Lastly, our results underline that PSD profile fingerprinting remains robust (97% accuracy) across multiple MEG recording session separated by a median of 160 days, unlike functional connectome fingerprinting (89% accuracy). Taken together, our results highlight consequential and stable individual differences in resting-state oscillatory activity and emphasize the importance of moving beyond population-level inferences while measuring neural activity.

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4-B "The Interaction Between Circadian Disruption and a Neurodevelopmental Risk Factor for Schizophrenia"

Tara Delorme, Lalit Srivastava and Nicolas Cermakian

Schizophrenia is a multifactorial disorder caused by a combination of inherited genes, and exposure to environmental insults. Insults that occur during critical periods of brain development are thought to be most detrimental and can lead to lifelong neurodevelopmental impairments. We are interested in maternal immune activation (mIA) at embryonic day 9.5, a model for a neurodevelopmental risk factor for schizophrenia, and its interaction with circadian rhythm disruption (CRD), a hypothesized risk factor for schizophrenia. Firstly, we hypothesized that mIA and CRD would act synergistically to affect schizophrenia-like behavioural impairments in mice. Baseline behaviour was measured after a standard light/dark cycle (12:12LD). Behaviour was tested a second time after constant light exposure (LL; known to disrupt circadian rhythms), and finally a third time after a second exposure to 12:12LD to serve as a light 'rescue'. Adult mIA male and female offspring did not differ from controls in general locomotion or in the elevated plus maze task. In a social interaction task, adult mIA males had less preference for a stranger mouse compared to an object than controls, with a larger effect after LL treatment. In prepulse inhibition, male and female mice showed overall sensory-motor deficits but no interaction with lighting condition. Secondly, we hypothesized that adult mIA-exposed offspring had impaired circadian rhythmicity, akin to patients with schizophrenia. To test this, mice were placed into running wheels and exposed to 3 different light challenges (12:12LD, LL and constant dark). Adult mIA-exposed offspring consistently showed more activity during the light phase than controls, while having no difference in dark phase or total activity. To conclude, mIA and CRD likely act synergistically to affect schizophrenia-like behavioural impairments. Discovering more efficient therapeutic options for patients may rely on uncovering the complex mechanisms in which these risk factors for schizophrenia interact to jointly exert their effect.

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4-C "Functional crosstalks between adrenergic and purinergic receptors in microglia"

Thomas Deluc, Ariel Ase and Philippe Séguéla

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Background: Neuropathic pain typically occurs after nerve injury and is characterized by persistent pain with no effective treatment. Microglia have received much attention in the past decade due to their importance in chronic pain. Microglia are in constant survey of the environment and are the first elements to respond after any kind of disturbance in the CNS. Microglia can detect danger signals, reach the damaged cells and become activated. Adenosine triphosphate (ATP), which is released after damage can act as a danger signal, and its concentration is increased in neuropathic pain. ATP can be recognized by the microglia due to the presence of purinergic receptors. Purinergic receptors (P2 receptors) are composed of 7 ionotropic receptors and 8 metabotropic receptors which are widely expressed in the body and have different important functions. It has been shown that the main purinergic receptors expressed in microglia, i.e. P2X4, P2X7, P2Y6 and P2Y12, play an important role in pain sensitization and in the maintenance of neuropathic pain. However, how these receptors are modulated is still poorly understood. Our goal is to investigate potential pathways involved in the modulation of microglial purinergic receptors in pain circuits. One interesting candidate is the Gs protein-coupled β2 adrenergic receptor. Noradrenergic descending fibers originating from the locus coeruleus are activated in response to painful stimuli and mediate spinal antinociceptive effects. As the expression of the β2 adrenergic receptor in the CNS is mainly limited to microglia, it represents a promising candidate regarding a functional crosstalk with microglial purinergic receptors relevant to pain mechanisms.

Methods: In order to investigate a possible modulatory effect of β2 adrenergic receptors on purinergic microglial receptors, we used the BV2 mouse microglial cell line and primary microglia isolated from the mouse forebrain (P1). Fura2-based ratiometric calcium imaging experiments were performed in order to validate the expression of the different P2 receptor subtypes in microglia and then to assess their possible crosstalk with β2 adrenergic receptors.

Results: Our calcium imaging data show that activation of the β2 adrenergic receptor modulates purinergic microglial receptors. β2 adrenergic receptors can potentiate the response of the ionotropic P2X7 ATP receptor involved in release of pro-inflammatory cytokines and can also inhibit the response of the metabotropic P2Y6 UDP receptor involved in phagocytosis.

Conclusions: The β2 adrenergic receptor can positively modulate (potentiate) the

response of P2X7 receptors and can negatively modulate (inhibit) the response of P2Y6 receptors. Further, we plan to confirm these results in human microglia (IPSC-derived or primaries) and also investigate which basic microglial functions are regulated by these crosstalks (cytokine release, phagocytosis).

Support: CIHR, LAEF, FRQS-QPRN

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4-D "Dynamic functional connectivity properties are differentially affected by anesthesia protocols and compare across species"

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Functional magnetic resonance imaging (fMRI) in rodents is an emerging field that allows for examination of brain networks in a preclinical setting[1]. To maintain stable experimental conditions, animals are typically sedated during acquisition[1]. However, the choice of anesthetic regimens impacts functional connectivity (FC) measures as defined by the temporal dependence of brain activity between distinct regions[2]. Determining which anesthetic regimen best conserves natural FC is an ongoing field of investigation. There has been growing support for the idea that treating FC as a constant property does not fully describe the complex spatio-temporal organization of FC between brain areas, but instead, that FC undergoes global reorganization over time, a property referred to as dynamic FC (dFC)[3]. Anesthesia reduces the complexity of these global dynamics[4–6], suggesting that greater dFC is reflective of conserved brain dynamics. In this work, we investigated markers of conserved brain dynamics through comparison of dFC properties in mice with different anesthetic regimens and in standard human fMRI.

We found group differences in the temporal variability in FC that might distinguish anesthesia regimens based on the conservation of brain dynamics. We further demonstrate that richer FC variability is not random, but tends to be captured by coordinated patterns of covariance described using principal component analysis. Finally, we identified that static measures of FC, the current gold standard for FC studies, is tightly related to underlying dFC properties, and this relationship holds in mice across anesthesia regimen as well as in humans.

This work demonstrates for the first time that dFC properties can be differentially affected depending on the choice of anesthesia protocols in mouse fMRI experiments. Perhaps most importantly, our results provide evidence that dFC can reveal novel information about brain dynamics which wouldn't be captured by standard FC measurements, and hence, stresses the importance of unraveling the contributions of these processes to the organization of major brain networks.

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5-A “The exosomal microRNA signature of degenerating human iPSC-derived neurons"

Sienna Drake, Cecilia Rocha, Thomas Durcan, and Alyson Fournier

Neurons and axons experience a variety of environmental stressors in neurodegenerative diseases. In multiple sclerosis, multiple mechanisms have been linked to alterations in neuronal health including glutamate excitotoxicity, iron dys-homeostasis, and oxidative stress. These can result in swelling and fragmentation of neurites and changes in gene expression within the neuron. Neurodegeneration is the best-known correlate for clinical disease in MS, however for progressive MS which is typified by steadily increasing disease burden, there are neither neuroprotective therapies nor prognostic tests informing long-term disease outcomes. MicroRNAs (miRNA) are small non-coding RNAs that mediate RNA interference gene silencing of messenger RNAs. Interestingly, they are stable outside of cells and are preferentially packaged into exosomes for transport outside of cells. They can be found in abundance in patient blood samples. Many studies have identified changes in the miRNA signature of multiple sclerosis patients however it is difficult to relate these changes to the disease pathology. Therefore, we are using in vitro neurodegeneration assays in human IPSC-derived cortical neurons to identify changes in the exosomal miRNA signature in neurons experiencing environmental stressors. We can then correlate these to what is already known in the literature about miRNA dysregulation in MS to identify key miRNA species that may implicate neurodegenerative processes in the disease progression. Ultimately we aim to identify miRNAs correlated to neurodegeneration that can be used to help assess and predict a patient’s prognostic disease course, and potentially inform neuroprotective therapies for progressive MS.

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5-B "Do histone deacetylase inhibitors enhance the heat shock response in motor neurons alone or in combination with arimoclomol?"

Fernandez M, Kuta R, Larochelle N, Minotti S, Nalbantoglu J, Durham HD

Upregulation of heat shock proteins (HSP) is one promising strategy to alleviate the disturbance in proteostasis caused by protein misfolding and aggregation, a common feature of Amyotrophic Lateral Sclerosis (ALS) pathogenesis. Motor neurons are relative resistant to stress-induced upregulation of HSPs, a property exacerbated with disease progression due to chromatin remodeling.

The purpose of this study was to determine if histone deacetylase (HDAC) inhibitors reduce the threshold for activation of the heat shock response in motor neurons and enhance the efficacy of HSP inducing drugs.

Arimoclomol potentiate HSP induction by stress. In dissociated cultures of murine spinal cord-dorsal root ganglia exposed to heat shock stress, the pan HDAC inhibitor, suberanilohydroxamic acid (SAHA), the HDAC1/3 inhibitor RGFP109, and HDAC6 inhibitor Tubastatin A increased expression of stress-inducible Hsp70 (HSPA1A) in motor neurons and amplified arimoclomol-induced Hsp70 expression. A different pattern was observed in culture models of familial ALS produced by expression of mutant SOD1, a model of proteotoxic stress, or mutant FUS, an RNA binding protein. Arimoclomol, had a small effect inducing Hsp70 in motor neurons expressing SOD1G93A that was enhanced by SAHA and RGFP109; SAHA and RGFP109 alone acted as co-inducers of Hsp70, But Tubastatin A was ineffective. The heat shock response was completely suppressed by mutant FUS and was not restored by HDAC inhibitors. However, through other mechanisms, SAHA, RGFP109 and surprisingly arimoclomol did reduce loss of nuclear FUS, a disease hallmark.

This study supports combination therapy of arimoclomol with a Class I HDAC inhibitor to improve neuroprotection through multiple mechanisms.

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5-C “Aging mice show motor deterioration and Purkinje cell firing alterations”

Eviatar Fields, Alanna Watt

McGill University

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 gait, and its Purkinje cells fire spontaneous action potentials at high frequencies which is disrupted in mouse models of ataxia. 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, 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 pathophysiology. Our current experiments focus on rescuing the reduced rates of firing in aged Purkinje cells with the goal of restoring motor coordination in aged mice.

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5-D "Stress-Induced Changes In Glutamate Receptor Binding: A PET Study With [11C]ABP688"

Marie Fitoussi[1], Atsuko Nagano-Saito[1], Kelly Smart[1], Peter Kang[2], Dana Goerzen[3], Jamie Near[3], Arguel Aguilar-Valles[4], Pedro Rosa-Neto[2,3], Marco Leyton[1,5], Chawki Benkelfat[1,5]

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Background: Abnormal glutamate transmission is involved in various stress-related disorders. A non invasive method for in vivo quantification of endogenous glutamate release in the human brain would be valuable to help uncover the role of glutamate in disease states and in response to therapeutic interventions. [11C]ABP688 is a highly selective antagonist that binds to an allosteric site of the metabotropic glutamate receptor type 5. Pharmacological challenges have raised the possibility that this ligand might be sensitive to acute glutamate fluctuations. Here, we explored the sensitivity of this PET ligand to changes in glutamate levels after an environmental change. For this, we administrated a stressful stimulus know to induce changes in glutamate turnover as measured by MRS. This would be reflected in reductions in ligand binding to mGlur5.

Methods: PET [11C]ABP688 dynamic acquisitions were conducted in of 4 male and 4 female healthy volunteers with a high‐resolution research tomography (HRRT). Scans, including MRS, were acquired at least 3 days apart, either after a stressful task or rest. The acute stressful stimuli consist in the administration of a 6 min intermittent, pseudo-randomized mild electric shock to the wrist. Time activity curves were extracted, and non-displaceable binding potential (BPND) was calculated by the use of the simplified reference tissue model. Mood and physiological parameters were measured throughout.

Results: Stress was associated with significant increase in sympathetic stress response, but this was not reflected by significant changes in MRS Glx/Cr nor Glu/Cr levels. Session x Subregion x Hemisphere ANOVAs for cortical (3 subregions), striatal (3 subregions), and limbic regions (2 subregions) yielded no effects of session nor interactions. However, regional percent change in BPND indicated a global tendency of increase at stress. BPND values at stress within 5 ROIs, but not magnitude of change, were positively correlated with extent of change in Glu:Glx ratio in the ACC. No correlations were found with other

physiological parameters.

Discussion: Glu:Glx reduction reflects glutamate reuptake following excitatory neurotransmission. The observed direction of the effect on [11C]ABP688 binding is the opposite of what has been predicted, and the change was within previous test-retest studies values. However, given the strong association with glutamate turnover measured by MRS, the sensitivity of the ligand to glutamate transmission cannot be discounted and requires further investigation.

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6-A "Spatial memory is protective against Alzheimer's Disease"

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Aim: The hippocampus (HPC) is critical for supporting memory functions, such as spatial memory, and a volume reduction in this structure is associated with future clinical diagnosis of Alzheimer's Disease (AD). Previous research in our laboratory demonstrated that spatial memory correlates to grey matter in the HPC. Moreover, MRI SNIPE grading measures in the HPC were previously shown to predict ensuing diagnosis of AD with a 73% accuracy. As such, the aim of the current study was to investigate whether spatial memory is protective against MRI AD pathology.

Methods: Seventy-four healthy older adults (43 female, 31 male; mean age: 65.5 ± 4.2 years) received MRI scans and SNIPE was used to compare their hippocampi to patients with AD versus controls. The MRI SNIPE measure involves computing the similarity of every hippocampal voxel of each participant to a library of manually segmented MRI datasets from the ADNI database consisting of equal numbers both healthy cognitively intact older adults and AD patients. Participants were tested on the Concurrent Spatial Discrimination Learning Task (CSDLT) and the Wayfinding task, both of which are sensitive to spatial memory and hippocampal grey matter. The CSDLT is a 12-arm radial maze in which participants have to learn the location of objects within pairs of arms, after which the presentation of arms is recombined but the reward contingency remains the same (stage 2). Stage 2 errors indicated whether the position of objects on the radial maze was learned in relation to the landmarks in the environment. The wayfinding task measures the ability to build and use a cognitive map of a virtual environment containing landmarks (e.g. pool, shop, etc.). Probe errors measure the participant's ability to find target locations in a straight path in the virtual town, hence measuring spatial memory.

Results: General linear modelling was used to regress spatial memory and age on SNIPE scores in men and women separately. Results showed that performance on the wayfinding task significantly predicted hippocampal SNIPE grading scores in men ($\beta = 0.493$, $p < 0.01$). The CSDLT task positively predicted hippocampal SNIPE grading scores in women ($\beta = -0.318$, $p < 0.05$).

Conclusion: The current study shows that participants with a good spatial memory have higher SNIPE scores, which are predictive of healthy cognition in normal aging. On the other hand, poor spatial memory is associated with lower SNIPE grading in the HPC, which is predictive of increased risk of future AD diagnoses. Sex differences in navigation may help explain differences in the

sensitivity of navigation tests to the MRI measures for men and women.

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6-B “Salivary HO-1 levels in Parkinson disease patients”

Julia Galindez, Lamin Juwara, Marisa Cressatti, Mervyn Gornitsky, Ana M. Velly, Hyman M. Schipper

Parkinson disease (PD) is the second most common movement disorder among adults and affects 2% of the population above 65 years of age. PD is characterized by progressive degeneration of dopaminergic neurons and formation of fibrillar inclusions (Lewy bodies) in subcortical brain regions involved in motor and certain non-motor functions. Heme oxygenase-1 (HO-1) is a stress protein that has been implicated in the pathogenesis of PD. HO-1 catalyzes the breakdown of heme to free iron, carbon monoxide and biliverdin (later converted to bilirubin by biliverdin reductase). While in the normal brain, protein expression of HO-1 is low and restricted to a small population of neurons and glia, HO-1 hyperactivity can be observed in several disease states. In PD, HO-1is overexpressed in astrocytes of the substantia nigra and decorates pathological Lewy bodies in affected dopamine neurons. In 2018, full-length HO-1 protein was detected in saliva of healthy individuals and PD patients for the first time. Here we show significantly decreased mean logarithmic-transformed HO-1/total protein in PD saliva (mean (SD): 4.15 (0.60); n=31) in comparison to non-neurological controls (4.76 (0.67); n=30; $p<0.001$) after adjusting by age, sex and relevant comorbidities. Individuals with decreased salivary HO-1: total protein have a higher likelihood of having PD (OR: 0.197; CI: 0.0708-0.5486). These results implicate salivary log-transformed HO-1/total protein as a potential biomarker to distinguish PD patients from non-neurological controls.

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6-C "Sildenafil improves cerebellar white matter and synaptic transmission following neonatal hypoxia-ischemia"

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Introduction: The cerebellum is increasingly being recognized as an important component of the brain and preliminary studies have shown that the cerebellum is also injured following hypoxia-ischemia (HI). Sildenafil has been shown to have promising neurorestorative effects in an animal model of HIE in the cortex. The objective of this study was to better understand the injuries to the cerebellum following hypoxia-ischemia (HI) and to further determine whether sildenafil may also improve these injuries.

Methods: HI was induced in Long-Evans rat pups at post-natal day 10 (P10) by a left carotid ligation followed by a 2-hour exposure to 8% oxygen; sham operated rat pups were used as a control. HI rats were randomly assigned to sildenafil (50 mg/kg) or placebo every 12 hours for 7 days, starting 12 hours after HI. The animals were sacrificed at P12, P17, and P30 and the cerebellum were extracted. Western blot analyses were performed, using markers for axon myelination (myelin basic protein, MBP), oligodendrocytes (oligodendrocyte lineage transcription factor 2, Olig2), and synaptic transmission (synaptophysin).

Results: Rat pups exposed to HI demonstrated significantly decreased expression of MBP ($p < 0.05$) and Olig2 ($p < 0.01$); sildenafil treatment reverted expression of these markers back to sham levels. HI rats also displayed a lower expression of synaptophysin; HI animals treated with sildenafil had significantly higher levels of synaptophysin ($p < 0.05$) than HI animals treated with placebo.

Conclusion: HI impacts axonal myelination and synaptic transmission in the cerebellum; both appear improved after sildenafil treatment.

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6-D "Optogenetically eliciting precisely-timed action potentials in cerebellar Purkinje cell axons"

Kim Gruver and Alanna Watt

Department of Biology, Integrated Program in Neuroscience

Optogenetics is a state-of-the-art tool for interrogating neural circuits. In the cerebellum, Purkinje cells serve as the sole output of the cerebellar cortex where they synapse on neurons in the deep cerebellar nuclei (DCN). To investigate the properties of this synaptic connection, we sought to elicit time-locked single action potentials in Purkinje cells. We used transgenic mice expressing channelrhodopsin-2 (ChR2) under the pcp2 promoter targeting Purkinje cells and optically activated ChR2 with a patterned spatial illuminator and blue light from an LED (470 nm). To optimize axonal ChR2-stimulation, we used whole-cell patch clamp recordings of ChR2-expressing Purkinje cells from acute cerebellar slices to determine the conditions that were necessary for robustly and reliably eliciting single action potentials. We compared ChR2-stimulation in axons and cell bodies from individual Purkinje cells and found that a longer light pulse was necessary to elicit single action potentials from axons. To explore axonal ChR2-stimulation conditions further, we exposed cells to ambient light prior to optogenetic activation and found that this caused both cell bodies and axons to be less sensitive to focused optogenetic activation. However, axons were nearly two-fold more affected than cell bodies. Finally, using our empirically-determined optimal axonal ChR2-stimulation, we elicited time-locked IPSCs in DCN neurons with minimal jitter. This allows us to optogenetically explore Purkinje cell connectivity in the cerebellum.

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7-A "White Matter Tractography and its Association with Verbal Memory among First-Episode Psychosis Patients"

Charlie Henri-Bellemare[1], Raihaan Patel[1], Katie Lavigne[1], M. Mallar Chakravarty[1], Martin Lepage[1]

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Background: Verbal memory is one of the most affected cognitive domains in patients with schizophrenia and related psychoses. Several studies have found associations between cognitive abilities and white matter fractional anisotropy (FA) in schizophrenia; however, only a few tractography studies have investigated FA relative to verbal memory in patients with a first-episode of psychosis (FEP) compared with healthy controls (HC). Although white matter tractography differences have been well established between chronic patients and HC, direction of findings from FEP studies have been inconsistent. Thus, the present study aims to examine whole-brain white matter differences and its association with verbal memory in individuals with a FEP relative to HC using tractography.

Methods: Diffusion-weighted images were acquired on a 1.5T scanner for patients (n=65) and controls (n=54) at baseline. The Wechsler Memory Scale [1] was used as a measure of verbal memory. Pre-processing was performed on a subject-by-subject basis using MRtrix (Brain Research Institute, Melbourne, Australia, http://www.mrtrix.org version 3) [2]. Diffusion tractography was generated using a probabilistic anatomically-constrained tractography algorithm [3], which constrains the reconstruction to specific biological priors. Furthermore, the spherical-deconvolution informed filtering of tractograms (SIFT) tool will be used to ensure the tractogram is biologically meaningful. This results in subject-specific connectomes defining the mean FA between two regions of interest that were defined using the Desikan-Killiany atlas. A linear model was used to test for main effects of group and main effect of verbal memory on white matter tract FA, covarying for age and sex. For both sets of analyses, results were corrected for multiple comparisons using false discovery rate (FDR).

Results: A significant main effect of group on whole-brain average FA was observed, with patients displaying lower average FA compared to healthy controls (Patients=0.291, controls=0.300, $p<0.05$). Whole-brain white matter tract FA analysis revealed that there are widespread differences between controls and individuals with a FEP. Group most strongly predicted white matter tract FA differences between left caudal anterior cingulate and left lateral orbitofrontal (patients mean FA=0.302, controls mean FA=0.342), left hippocampus and right isthmus cingulate (patient mean FA= 0.217 controls mean FA= 0.318), and finally left lingual and left rostral anterior cingulate (patients mean FA=0.162, controls mean FA= 0.249. However, none survived correction for multiple comparisons. Further, there was no significant association between verbal memory and white

matter tract FA in FEP or HC.

Discussion: Findings from this study suggest there are some significant differences in whole-brain average FA between individuals experiencing a FEP and healthy controls. However, when analyzing whole-brain tract FA, none of the connections survived corrections for multiple comparisons. These findings might be limited by the scanner resolution included in this study, which may not capture more subtle differences. Nonetheless, these results are consistent with a cross-sectional study comparing healthy individuals to chronic and first-episode patients suggesting that modest differences are present early in the disease and increase as the disease progresses [4]. We suggest that future studies analyze white matter tract using a longitudinal design to identify disease progression.

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7-B "Environmental Enrichment during Peri-Adolescence, but not Young Adulthood, Increases Resistance to Subchronic Variable Stress in Female Mice"

Leora Hiar, Kelly Craig, Carine Parent, Allison Martel, Xianglan Wen, Josie Diorio, Tie-Yuan Zhang

While stressful events can lead to mental health problems, not everyone who experiences stress will develop psychopathologies. Early life experiences are associated with individual differences in stress reactivity. Previous research has shown that enrichment in both the peri-adolescence and young adulthood periods promotes resiliency to chronic social defeat stress in male mice. However, it is not known whether enrichment during development affects stress resiliency in females. We studied the effects of enrichment in peri-adolescence (postnatal day 21) or young adulthood (postnatal day 45) on the response to six days of subchronic variable stress. Young adult enrichment does not protect against an increase in anxiety-like behaviour after subchronic variable stress. In contrast, peri-adolescent enrichment significantly reduced the proportion of mice with anxiety-like behaviour. These result suggest that interventions aimed to reduce stress reactivity and improve health outcomes in females should start early in the adolescent period.

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7-C "Profiling exosomes in the anterior cingulate cortex of individuals with major depressive disorder"

Pascal Ibrahim[1,2], Corina Nagy[2], Saumeh Saeedi[2,3], Jean-Francois Theroux[2], Gustavo Turecki[1,4]

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Background: Major Depressive Disorder (MDD) is one of the leading causes of disability worldwide, affecting 20% of the population. With our limited understanding of processes underlying the depressive state in the brain, the magnitude of this problem will continue to grow. The environment has been thought to play a role in the disease development, resulting in biological changes mediated by epigenetic mechanisms. MicroRNA's (miRNA) are well known epigenetic regulators that have recently been found to be packaged into exosomes, which are small extracellular vesicles of endosomal origin. Exosomes have emerged as means of intercellular communication, a process that is also disrupted in the brain in the depressed state. They are thought to transfer miRNA between cells, and this can alter gene expression in recipient cells. Therefore, we hypothesize that exosomal cargo is altered in MDD patients compared to healthy controls. Our aim is to extract exosomes from human post-mortem prefrontal cortex, a region previously associated with depression, and profile the exosomal cargo. We will then attempt to elucidate miRNA's that are differentially expressed between MDD patients and healthy controls.

Methods: Post-mortem brain tissue from the prefrontal-cortex was mildly dissociated in the presence of collagenase type III. Residual tissue, cells, and large vesicles were removed, and exosomes were extracted using size exclusion chromatography. The quality was assessed by western blots, probing for Calnexin, BiP, VDAC, TSG101, and CD9, and by transmission electron microscopy (TEM). A small RNA library was constructed and sequenced using the Illumina Platform to assess the quality as well.

Results: Western blots confirmed the presence of endosomal and exosomal markers (TSG101, CD9), respectively, and little to no ER (Calnexin), Golgi (BiP), or mitochondria (VDAC) contamination. TEM images showed typical cup-shaped morphology within the expected size range (30-150 nm). Sequencing results revealed miRNA and mRNA relevant to both exosomes and brain function.

Conclusions: High quality exosome extractions can be obtained from post-mortem brain tissue using our method. We will proceed with extractions from 20

MDD patients and 20 psychiatrically healthy controls to profile the exosomal content and compare between groups. This will be the first study to profile brain-derived exosomes in the context of depression. This will provide novel mechanistic insights into the pathophysiology of MDD and will serve as a starting point to examine the potential role of exosomes in MDD pathology.

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7-D "Novel roles of Neurexin and Neuroligin in the Borderless pathway controlling visual circuit function"

Arianna Izawa-Ishiguro, Hunter Shaw, Wen-Tzu Chang, Yong Rao

Synapses represent the primary units of a neural circuit, in which cell-adhesion molecules can mediate the formation of complex connections between various neurons. These molecules are often evolutionarily conserved among invertebrate and vertebrate systems, such that their roles and interactions may be orthologous from one model species to another. The *Drosophila melanogaster* visual system is an excellent model for investigating the intricacies of neuronal connectivity and synaptic function, given its relative structural simplicity. Recent studies in our lab have identified Borderless (Bdl), an immunoglobulin (Ig) transmembrane protein of the IgSF9 family, as an important regulator in mediating specific recognition between R8 photoreceptor axons and their postsynaptic target neurons in the optic lobe. While doing so, Bdl has been modeled to promote axonal transport and proper localization of synaptic vesicles for R8 synaptic function and colour vision. However, the molecular mechanisms by which Bdl functions have yet to be determined. Due to preliminary results from our lab that strongly suggest an interaction between Bdl and another cell-adhesion molecule, Neuroligin 2 (Nlg2), it is speculated that Bdl may mediate proper R8 synaptic function by interacting with Nlg2 and its trans-synaptic binding partner, Neurexin (Nrx). Loss-of-function analysis in *nrx-1* homozygous and hemizygous mutants indicate that Nrx is involved in proper synaptic vesicle localization, which is consistent with cell-type-specific *nrx-1* RNAi knockdown results. Interestingly, Nrx-1 appears to also have a role in R8 subtype specification, which is determined by the type of rhodopsin expressed in R8 photoreceptors. Loss-of-function and cell-type-specific RNAi knockdown analysis consistently indicate potential roles of Nrx-1 and R8 postsynaptic targets in influencing rhodopsin expression. Currently, our results support a model in which Nrx-1 may interact with Bdl and Nlg2 in mediating R8 synaptic vesicle localization, while likely influencing R8 photoreceptor subtype specification during visual circuitry development.

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8-A "Examination of Cell Type Populations and the Mesocortical Dopaminergic System in the Prefrontal Cortex in Chronic Neuropathic Pain"

HyungMo Kang[1,2,3], Lucas Topham[1,2,3], SeungHwan Lee[2,3], Michael Ogundeji[2,3], Magali Millecamps[2,3], Stephanie Gregoire[2,3], Laura S. Stone[2,3,4]

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Background: Chronic pain is debilitating, is often due to unknown causes, and is highly comorbid with affective and cognitive disorders. Despite continuous effort to improve patients' quality of life, a deeper understanding of the condition is desperately needed to improve the treatment efficacy. Many chronic pain conditions are associated with structural and functional alterations in the Prefrontal Cortex (PFC) along with other structures in the central nervous system. Dopamine, a monoamine neurotransmitter which plays critical roles in reward and motivation, is also crucially involved in pain. While its importance in chronic pain conditions has been well demonstrated in the mesolimbic system, the role of dopamine in the mesocortical system in the PFC and its implication in chronic pain have not been extensively studied. The goal of this time-course study is to determine if there are changes in populations of cell types (neurons, astrocytes, microglia), and in the dopaminergic system in the PFC using a mouse model of chronic neuropathic pain. The time-points of interest are 2-week (sub-chronic) and 6-month (chronic) post-injury.

Methods: To explore the possible mechanisms underlying pain-related structural and functional changes in the PFC, we evaluated structural changes by studying cell type populations, and functional changes by studying the mesocortical dopaminergic system in the PFC. Changes in the proportion or total neuronal, astrocytic and microglial cells, and the dopamine synthesis and degradation enzymes, Tyrosine Hydroxylase (TH) and Catechol-O-Methyltransferase (COMT) were quantified using Fluorescent Immunohistochemistry and Western Blot analysis.

Results: At both 2-weeks and 6-months post-nerve injury, there were no significant changes in cell populations in the PFC. TH expression was significantly decreased at 2-week but not at 6-month postinjury, but COMT expression was not significantly changed at either time-point in the PFC.

Conclusion: These data suggest that pain-related structural changes in the PFC are unlikely due to a significant shift in specific cell type populations, and that maladaptive plasticity in mesocortical dopaminergic system may vary with duration of pain.

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8-B "Characterization of Somatic Mutations in mTOR Pathway Genes in Focal Cortical Dysplasias"

Eric Krochmalnek[1,2], Andrea Accogli[3], Judith St-Onge[2], Nassima Addour[2], Roy Dudley[4], Kenneth Myers[3,4], François Dubeau[4], Jason Karamchandani[5], Jean-Pierre Farmer[4], Jeffrey Atkinson[4], Jeffrey Hall[4], Chantal Poulin[3,4], Bernard Rosenblatt[3,4], Joël Lafond Lapalme[2], Steffen Albrecht[5], Jean-Baptiste Rivière[2], and Myriam Srour[3].

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Background: Focal cortical dysplasias (FCDs) are congenital structural abnormalities of the brain and represent the most common cause of medication-resistant focal epilepsy in children and adults. When possible, surgical resection of affected tissue is performed as treatment. Recent studies have shown that somatic mutations, which are embryonic mutations arising after fertilization, underlie some FCD cases. To date, these somatic mutations have been found in genes of the mTOR pathway, an intracellular signaling pathway important for cell cycle regulation and migration. Specific therapies targeting the mTOR pathway are presently available, allowing for potential personalized treatment. However, testing for somatic mTOR pathway mutations in FCD tissue is not performed on a clinical basis, and the contribution of such mutations to the pathogenesis of FCD remains unknown.

Aim: Our objective is to investigate the feasibility of screening for somatic mutations in FCD tissue and to determine the proportion of FCDs which are due to low-level somatic mutations in mTOR pathway genes. Furthermore, we will determine for each patient the spatial distribution of mTOR mutations throughout resected FCD tissues.

Methods: We performed ultra-deep sequencing of 13 genes belonging to the mTOR pathway using a custom HaloPlexHS target enrichment kit (Agilent Technologies) in 16 resected, histologically-confirmed FCD specimens.

Results: We identified causal variants in 62.5% (10/16) of patients at an alternate allele frequency of 0.75–33.7%. Distribution of the mutation loads correlated with the size of the FCD lesions and the severity of the histopathological abnormalities.

Conclusions: Screening mTOR pathway genes in resected FCDs using a custom panel results in a high yield, is feasible in a clinical setting, and should be considered given the important potential implications regarding surgical

resection, medical management and genetic counselling.

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8-C "Linking increased chronic stress-related memory and stress susceptibility in an animal model of depression"

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Introduction: Depression is a debilitating mood disorder affecting 300 million individuals worldwide and was named the leading cause of disability by the World Health Organization. Exposure to chronic stress is one of the factors known to precipitate depression. Clinical research has shown that when exposed to stress, certain individuals have greater difficulties coping with it compared to others. The neural basis which underlies the vulnerability to depression provoked by chronic stress remains unclear. However, cognitive changes, particularly a bias towards the encoding and recall of memories of negative events has been described in depression and suggested to underlie such a vulnerability. We proposed that the hippocampus, specifically the dorsal CA1 hippocampal subregion, is a promising region of interest which links the effects of chronic stress with cognitive changes in depression. The hippocampus has been highly implicated in the pathogenesis and treatment of depression, but also plays a central role in the encoding and recall of salient information related to stress.

Method: The UCLA miniscope was used to examine the activity of dorsal CA1 neurons in C57 mice that are susceptible to a chronic social defeat stressor (8 daily episodes of social defeat by an aggressive CD1 mouse). Through a lens implanted in the hippocampus, the miniscope enables for the recording of fluorescent calcium activity as a proxy for neuronal activation. A social interaction test determines susceptibility, as such animals express avoidance of a social encounter with the aggressor. We examined the progressive change of the activity of individual dorsal CA1 neurons during chronic stress. Additionally, we compared dorsal hippocampal activity during spontaneous social interaction bouts between the stressed C57 mouse and the aggressor, as social memory for the aggressor may determine the avoidance of this animal. Non-stressed mice and stressed mice that are resilient to chronic social defeat stress were used as controls.

Results: Increased calcium spiking frequency in the dorsal CA1 was observed in susceptible animals as the days of the chronic stress paradigm progressed. Interestingly, spiking frequency was similar to resilient and control animals at the beginning of defeat, but the observed progressive increase reached significance on the last defeat day (5th defeat, $p=0.01$; 8th defeat, $p=0.04$). Furthermore, neurons that were active during stress were significantly reactivated on

subsequent stress days in susceptible animals ($p=0.03$). Lastly, we identified neurons active during spontaneous bouts of social interaction with an aggressor and found that susceptible animals demonstrated increased spiking frequency of these ‘social interaction’ neurons when compared to resilient and control mice.

Conclusion: The susceptibility to a chronic stressor is potentially due to increased activity of defeat-related neurons and recall of the defeat memory. Enhanced formation of such a chronic stress-related social memory may be a cellular mechanism for stress susceptibility and the vulnerability to depression.

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8-D “Structural Brain Connectivity Predicts Longitudinal Amyloid Beta Deposition in AutosomalDominant Alzheimer’s Disease Mutation Carriers”

Elizabeth Levitis, Jacob W. Vogel, Thomas Funck, Gregory Kiar, Yasser Iturria-Medina, Alan C. Evans

Alzheimer’s disease is characterized by the presence of Amyloid-Beta (AB) plaques comprised of the misfolded protein. The lack of a mechanistic understanding of the spatiotemporal spread of AB prompted the development of an epidemic spreading model (ESM) which modeled the spread of the protein along the brain’s structural connections as a function of the brain’s clearance response and infectious spreading like dynamics. AD has two primary forms - the most common form being sporadic AD and the much rarer autosomal dominant AD. In ADAD mutation carriers will invariably develop dementia, and the onset of dementia symptoms can be estimated using the age of parental onset. Previous application of the model to patients with sporadic AD and controls pointed to impaired clearance as a key contributor to AB accumulation, implicating vascular dysregulation as a feature of AD. Here, we aimed to apply the ESM to a cohort of ADAD mutation carriers, to determine whether the model can accurately simulate AB deposition and to compare the mechanisms driving AB propagation between the two types of AD. Using the ESM, we were able to simulate baseline global AB deposition probabilities of mutation carriers with similar accuracy to the original study and using the same AB seed regions previously identified - namely, the caudal anterior cingulate and posterior cingulate. We built off of the original implementation of the ESM by fitting it to each subject’s baseline AB deposition probabilities to simulate the probabilities at the second timepoint. Model accuracy was assessed by comparing the actual and predicted individual rate of change between timepoints. To further validate the estimated model parameters, we tried to predict the third timepoint using the second timepoint as the baseline and have been able to do so with mixed results. Our current findings warrant further exploration of the association between genomic and clinical attributes and model performance.

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9-A "Investigation of the Positron-Emission Tomography [18F]MK-6240 Tau Ligand in Genetic Frontotemporal Dementia"

Jake P. Levy, Melissa Savard, Tharick A. Pascoal, Elizabeth Finger, Jean-Paul Soucy, Pedro Rosa-Neto, and Simon Ducharme

Background/Objectives: Tau is one of several proteins which can pathologically aggregate and cause frontotemporal dementia (FTD). While knowing which protein is causing a patient's disease is crucial – particularly for recruiting patients for trials of anti-tau drugs and tracking their progression – no biomarker currently exists for identifying the pathogenic protein in vivo. The objective of this project is to investigate the potential for the MK-6240 PET tracer to bind to tau in FTD. Importantly, recent studies have suggested that MK-6240 binds effectively to tau in Alzheimer's disease (AD), but results have been negative thus far outside of AD.

Methods/Overview: We are currently enrolling subjects with genetic FTD, who constitute an ideal population for testing because their pathology is already known. Each participant recruited so far was submitted to tau-PET scanning with MK-6240, amyloid-PET imaging with NAV-4694 to rule out confounding AD pathology, high-resolution structural MRI, and a full battery of neuropsychological tests. We are scanning patients with MAPT mutations (which cause accumulation of tau leading to FTD; therefore these patients are expected to show tau binding) as well as patients with FTD due to mutations such as C9orf72, GRN, and VCP (which cause accumulation of TDP-43; thus these patients act as disease controls without tau and are expected to not show abnormal MK-6240 binding). Images were processed using a previously validated pipeline; MK-6240 standard uptake value ratios from 90-110 minutes were calculated for both anatomical regions of interest and voxel-by-voxel maps using cerebellum gray matter as a reference region.

Results: We have at this point obtained results from seven patients. We have scanned three symptomatic MAPT patients, whose tau-PET scans all demonstrated binding in expected regions (eg. orbitofrontal cortex, temporal lobes, basal ganglia, etc.) without significant off-target binding. We also analysed two asymptomatic MAPT carriers: one, estimated to be five years from disease onset, showed MK-6240 binding especially in anterior frontal and medial temporal lobes; the other was approximately 30 years from disease onset and did not demonstrate any binding. We additionally scanned two individuals with symptomatic FTD caused by a non-tau mutation (one C9orf72; one VCP): their scans both did not reveal any MK-6240 binding, suggesting their disease is caused by something other than tau. All seven amyloid-PET scans were negative.

Conclusions: Our findings of MK-6240 binding specifically in regions known to be implicated in FTD in three symptomatic MAPT patients and one asymptomatic

MAPT carrier within five years of disease onset are promising, particularly when combined with the absence of binding in our participants with C9orf72 and VCP mutations (who are both not expected to have tau). Although preliminary, these results are encouraging for eventually developing a test for detecting tau in vivo in FTD. Further patient recruitment is ongoing to determine clinical applicability.

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9-B “Testosterone-Cortisol Ratio, Cortico-Amygdalar Structural Covariance and Cognition Across Childhood and Adolescence"

Jimin Lew, Sherri Lee Jones, Isobel Orfi, Charlotte Little, Kelly N Botteron, Simon Ducharme, James T McCracken, Tuong-Vi Nguyen

Cortisol and testosterone are the end products of two hormonal axes, the hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamic-pituitary-gonadal (HPG) axis. Testosterone, a sex-steroid hormone, has been shown to have both neuroprotective and neurotoxic effects, whereas cortisol, a glucocorticoid, displays primarily catabolic and neurotoxic properties. Both testosterone and cortisol have been shown to play a role in age-related cortical development throughout childhood and adolescence. Here, we examined the effect of the testosterone-cortisol (TC) ratio on amygdalar volume, cortical thickness, and cortico-amygdalar structural covariance in a longitudinal sample of typically-developing children and adolescents from ages 6-22. We also investigated associations between TC related cortico-amygdalar covariance, and cognitive and behavioral measures. Results indicated TC ratio was associated with cortical thickness of the superior parietal lobule (Broadmann Area 7; BA 7) and as well as visuo-amygdalar (BA 17/18) and somatosensory-amygdalar (BA 3/2/1) structural covariance. TC-related cortical thickness was associated with lower scores on tests of verbal working memory. In addition, TC-related structural covariance was associated with lower scores on tests of executive function, but with higher scores on tests of spatial working memory. Neither TC-related cortical thickness nor TC-related structural covariance was associated with behavioral measures. Thus, higher testosterone levels, relative to cortisol levels appear to result in a net increase in structural connections between the amygdala and visuo-somatosensory areas as well as a reduction in the age-dependent cortical thinning of the superior parietal lobule. This may in turn promote bottom-up, amygdala-dependent influences on the cortex which ultimately affect working memory and executive function.

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9-C "Univariate and multivariate regression models identify single nucleotide polymorphisms (SNPs) associated with anhedonia and fearfulness in rats"

Li Li, GyeongCheol Cho, ZiHan Wang, Oscar Vasquez, Maria Aristizabal, Nick O'Toole, Irina Pokhvisneva, Josie Diorio, Amsale Belay, HeungSun Hwang, Marla B Sokolowski, Tie Yuan Zhang, Michael J Meaney.

Genome-wide association studies identify risk genetic loci associated with pathophysiology of psychiatric disorders in human. However, current animal models of psychiatric disorders introduce extreme manipulations such targeted null mutations or overexpression, which do not reflect the subtle effects of SNPs on gene expression. We probed candidate regions of the outbred Long-Evans rat genome for single nucleotide polymorphisms (SNPs) associated with anhedonia and fearfulness using Sequenom sequencing. Using linear mixed – effect regression analysis, we found that rs198664367 (Ampk) and rs13448419 (Creb3l1) were significantly associated with total center time and latency to food in novelty suppressed feeding (NSF) test, respectively. Animals with CA genotype in Ampk gene show increased total center time compared to CC genotype. Animals with GC genotype in Creb3l1 gene show increased latency to food compared to GG genotype. Using genetics structural component analysis, we showed that Penk, Grm2, Creb/Creb3l2, and Ampk/Prkaa1 were significantly associated with total center time. Nap1/Nap1l4 was significantly associated with latency to food. Sdk2, Penk, Pka/Prkacb, and Fkbp5 were significantly associated with percentage sucrose preference. These findings provide preliminary evidence of SNP association with phenotypic outcomes in rats and provide a model for the study of the biological mechanisms underlying genotype – phenotype associations.

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9-D “Shedding light on topographic map formation with GCaMP-expressing Xenopustadpoles”

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

Sensory maps are known to undergo activity-dependent anatomical refinement during development, but little is known about functional changes in early maps. Because the *Xenopus laevis* retina responds to light even before retinal ganglion cell axons have arrived in the tectum, it permits the functional study of topographic map formation from very early stages. Tadpoles expressing the genetically-encoded calcium indicator GCaMP6 were obtained either by fertilizing eggs from albino frogs with sperm from elav:GCaMP6s transgenic frogs, or by microinjecting GCaMP6 mRNA into one blastomere of two-cell stage embryos. The latter approach results in half-mosaic tadpoles expressing GCaMP6 protein in all the postsynaptic tectal neurons on one side of the embryo and in the presynaptic retinal ganglion cell axons that project to the other side, allowing independent analysis of pre-and postsynaptic map maturation. Retinotopic maps were extracted by presenting monocular visual mapping stimuli while performing rapid 4D multiphoton calcium imaging throughout the tadpole optic tectum, then correlating fluorescence intensity changes to the positions of visual stimuli. The contributions of NMDA receptors to map refinement was tested by comparing maps in tadpoles reared in the NMDA receptor antagonist MK-801. We found that coarse retinotopic maps were already present at very early stages (NF stage 45). Rearing tadpoles in MK-801 did not prevent the overall emergence of retinotopic maps, but significantly perturbed fine-scale map organization.

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10-A "Fragmented Maternal Care Caused by Early Life Stress Abolishes BMAL1 Rhythm in the Hypothalamic Suprachiasmatic Nucleus Of the Neonatal Offspring"

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Central and peripheral circadian clocks are responsible for generating 24h rhythms for many important metabolic and physiological processes including sleep-wake and feeding cycles. In the adult, the master clock in the suprachiasmatic nucleus (SCN) is very sensitive to light and modestly sensitive to food intake while another central oscillator in the dorsal medial hypothalamus (DMH) is profoundly affected by feeding schedule. In developing rodents, maternal cues and rhythmicity in maternal care synchronize rhythms in the SCN of offspring before they become sensitive to light. We hypothesized that fragmentation of maternal care by the early stress of limited bedding (LB) exposure would perturb the development of circadian rhythmicity in clock (BMAL1, Per1, Per2) gene expression in the SCN and DMH of preweaning rat pups on PND10. We observed that normal bedding (NB) pups displayed a trend for a significant BMAL1 rhythm in the SCN, peaking around CT18, which was abolished in LB pups. There was no significant BMAL1 rhythm in the DMH of either NB or LB pups suggesting that the DMH rhythm matures later than the SCN rhythm and is not affected by early stress. Expression of other clock genes in these regions is currently being investigated.

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10-B "Characterization of Vip Interneuron Plasticity in the Motor Cortex"

Amanda McFarlan[1,2], Chaim Weinernam[1], Maria Haddad[1], P. Jesper Sjöström[1]

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Most anti-epileptic drugs are thought to act via GABAergic neurotransmission mediated by inhibitory neurons (INs) to impact local activity. There are many IN types, of which vasoactive intestinal peptide-expressing (Vip) INs are particularly poorly described. For example, very little is known about Vip IN synaptic plasticity. Yet, Vip INs are known to have a key disinhibitory role by inhibiting nearby INs which increases seizure susceptibility and duration. Vip INs thus represent a promising seizure control point. We therefore set out to characterize mouse motor cortex Vip INs and their plasticity.

We bred transgenic mice that express Channelrhodopsin-2 (ChR2) in Vip INs by crossing Vip-Cre and ChR2 reporter mice (Ai32-flox). Using 2-photon imaging, Vip INs were targeted for whole-cell recording in acute slices and their electrophysiological properties were measured. Vip IN density across cortical layers was assessed by immunohistology. Vip IN spike threshold varied with cortical depth (layer 2/3: -40.3 ± 1. 6 mV, n=30 cells vs layer 5: -34.6 ± 1.8 mV, n=16, $p < 0.05$) with a consistently low rheobase current (74 ± 10 pA; n=46). Spike half width and height were 0.95 ± 0.04 ms and 44.0 ± 2.0 mV (n=46). Vip INs most densely populated L2/3 (52% ± 2%; n=7 animals), followed by L5 (24% ± 2%), L6 (17% ± 1%), L1 (3.4% ± 1%) and L4 (3.6% ± 1%, $p<0.001$). We are currently characterizing the plasticity of Vip IN connections onto Martinotti cells, with preliminary data suggesting that LTD arises from a repeated pattern of pre-before-post coincident firing while no change occurs following a repeated pattern of post-before-pre coincident firing. In conclusion, Vip IN outputs are plastic and may be possible to harness to alleviate seizures.

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10-C "Pediatric Age Acceleration: A Potential Biomarker of Individual Differences in the Legacy of Maternal Mental Health on Child Development"

Megan G. McGill, Lisa M. McEwen, Roseriet Beijers, Marieke Tollenaar, Irina Pokhvisneva, Michelle Kee, Matthew Oldach, Elika Garg, Neerja Karnani, Michael S. Kobor, Carolina de Weerth, Michael J. Meaney, Kieran J. O'Donnell

Background: Perinatal maternal anxiety is associated with adverse developmental outcomes that vary markedly at the level of the individual child. Currently, we lack a predictor for this exposure which depicts such variation. Epigenetic clocks provide an estimate of biological age on the basis of DNA methylation information across the genome. Epigenetic age acceleration (the difference between real and estimated age) has emerged as clinically relevant biomarker for adverse health outcomes in adults. The error of epigenetic clocks currently in use (≥3.6years) limits the use of these estimators in pediatric populations. A new epigenetic clock designed for use in children, the pediatric clock (error =0.35years), has been developed and shown to associate with child neurodevelopment. In this project, we used longitudinal DNA methylation data to examine how perinatal maternal anxiety associated with epigenetic aging in children. Further, we investigated gender differences in epigenetic aging at multiple time points.

Methods: DNA methylation data from our discovery cohort (GUSTO) of 200 children across 3 timepoints (3, 9, and 48 months) was used to calculate pediatric age acceleration estimates (AgeAccPedBE). Estimates from a second epigenetic clock, the multi-tissue epigenetic clock, were calculated to use as a benchmark for our analyses (AgeAcc353). A generalized estimating equation was used to investigate the association between maternal anxiety and pediatric epigenetic aging over time. AgeAccPedBE and AgeAcc353 estimates were generated in a replication cohort (BIBO) of 148 children at age 6 and 10 years. The generalized estimating equation was repeated with maternal prenatal anxiety. Gender, ethnicity, and cell type composition were covaried in our models. Both cohorts were stratified by gender at each timepoint and student's t-tests were used to assess differences in AgeAccPedBE and AgeAcc353.

Results: Our analyses indicated a significant association between increased prenatal maternal anxiety and accelerated aging over time in GUSTO. This association was observed using both AgeAccPedBE and AgeAcc353. This finding was replicated in BIBO using AgeAccPedBE, but not AgeAcc353. Across both cohorts, a stronger association was observed between maternal antenatal anxiety and AgeAccPedBE than estimates derived from the multi-tissue estimator. No significant differences were observed between males and females epigenetic aging in the GUSTO cohort. In the BIBO cohort, we see no significant difference at 6 years, and a significant difference at 10 years, such that females are aging significantly faster.

Discussion: Understanding the environmental factors that contribute to pediatric epigenetic aging will help provide a description of the regulation of epigenetic age in childhood. Future investigation into the predictive ability of the pediatric clock on childhood developmental outcomes such as school readiness will help to further assess the utility of this novel tool. The validation of this tool as a predictor of child developmental outcomes may have relevance for precision approaches in child and adolescent health. These analyses highlight the potential for the pediatric clock as a biomarker for variation in effects of maternal prenatal anxiety at the level of the individual child.

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10-D "Hypomyelination-related behavioural deficits caused by social isolation in juvenile mice"

Sarah McGillivray, Marius Tuznik, Gabriel Devenyi, Mallar Chakravarty, David Rudko, Christine Tardif

Myelin is a molecular bilayer composed of proteins and lipids, which stabilizes axons, facilitates neural communication via saltatory conduction, and supports neuron function and metabolism. It aids in the formation of stable networks during development, and remains plastic throughout the lifetime to adapt to an organism's environment. The relationship between experience and adaptive myelination can be exploited to better understand the dynamics of myelination across a lifetime. To do so, animal models are needed to first establish causality in the relationship between myelination and experience in the healthy brain. Social isolation is a form of deprivation paradigm used in mice to elicit hypomyelination in the prefrontal cortex (PFC), and a behavioural phenotype including decreased sociability, and increased anxiogenic behaviour. Behavioural implications of social isolation during the critical period of PFC development in juvenile mice was investigated with the goals of reproducing results of previous studies, investigating sex differences, and determining the capability of a magnetic resonance imaging protocol to detect myelination differences *in vivo*. Sexual dichotomy in vulnerability to social isolation was studied through the presentation of behavioural deficits. We found that isolated male mice ($n = 8$) show significantly higher anxiety-like behaviours ($t(17.025) = -3.44$, $p = 0.003$), as well as lower sociability compared to their socially-housed counterparts ($n = 12$) ($t(12.404) = 2.52$, $p = 0.027$). The behavioural phenotype of female mice ($n = 13$) is not significantly affected by two weeks of social isolation following weaning, however this may be a dose-dependent relationship in which a longer period of isolation results in the development of behavioural deficits similar to those seen in male mice. Magnetization transfer saturation imaging was used as a non-specific marker of myelin. Lower PFC myelination is expected in mice with behavioural deficits.

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11-A "The ocular dominance shift from short-term monocular deprivation is short-lived"

Seung Hyun Min, Alex S. Baldwin, Robert F. Hess

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Purpose: The objective of this study is to investigate the temporal and storage properties of visual plasticity induced by monocular deprivation in adults with normal vision. Monocular deprivation strengthens the deprived eye's contribution to binocular vision in adults with normal vision for a short duration in adults (Lunghi et al., doi: 10.1016/j.cub.2011.06.004). This effect has been shown with various visual tasks such as binocular competition (binocular rivalry tasks) and combination (Zhou et al., doi: doi: 10.1167/13.5.12). It has been shown that the effect of monocular deprivation lasts for only about 30 minutes in adults with normal vision (Zhou et al., doi: 10.1155/2017/4780876). We examine whether the ocular dominance changes induced by monocular deprivation can be more long-lasting after multiple rounds of monocular deprivation for five consecutive days.

Methods: Using a binocular phase combination task, we investigate whether this plasticity effect can accumulate across multiple periods of monocular deprivation. Ten adults with normal vision were tested on five consecutive days at a similar time each day. They performed the baseline measurement, were patched for 120 minutes using a translucent patch, and then completed the post-patching measurement tests at 0, 3, 6, 12, 24 and 48 minutes after patching.

Results: We conducted a 2-way (Before vs after patching x Day) mixed ANOVA and yielded no significant effect, $F(1, 4) = 4.242$, $p = 0.126$. Moreover, we compared the baseline of eye balance across days and found no significant effect between the baselines across days using 1-way mixed ANOVA, $F(1, 19) = 1.32$, $p = 0.26$. We also performed the Wilcoxon Signed Rank Test to compare the changes in ocular dominance between before and after patching and found no significant difference across days.

Conclusions: Our results show that, at least in normal adults, the neuroplastic changes caused by monocular deprivation are short-lived.

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11-B "Profiling m6A RNA Methylation in Human Postmortem Brain in Individuals with Depression"

Haruka Mitsuhashi[1,2], Corina Nagy[2], Zahia Aouabed[2], Gustavo Turecki[1,3]

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Introduction: Major Depressive Disorder (MDD) is one of the most common psychiatric disorders worldwide. Mounting evidence suggests there is an alteration of epigenetic mechanisms in response to stressful stimuli and environmental factors in the pathophysiology of MDD, yet little is known about the epitranscriptome in MDD. N6-methyladenosine (m6A) is the most abundant and reversible RNA modification in mammalian mRNA. Given its high abundance and dynamic regulation in the brain, m6A has been described to be crucial in brain development. Recent studies have found m6A to be involved in stress response suggesting its importance in the development of stress-related psychiatric disorders. However, there are no human studies examining m6A-seq in the brain and its role remains largely undescribed. The aim of this study is to describe the landscape of m6A in the human brain and to identify changes that may occur in the context of MDD.

Methods: To examine the post-mortem stability of m6A and the influence of age, RNA Integrity, and pH on m6A levels, global m6A levels were quantified using EpiQuik m6A RNA Methylation Quantification Kit (Epigentek). To assess the small quantity of RNA extracted from post-mortem brain tissue, a low-input m6A-seq protocol was optimized according to the published protocols and sequenced on the Illumina platform.

Results: Results suggest that PMI does not have a significant influence on global m6A levels and m6A is relatively stable in post-mortem brain. A significant number of peaks were detected using the low-input m6A-seq protocol compared to a high-input m6A-seq protocol.

Conclusions: The use of human postmortem brain could help us understand the role of m6A in general brain function as well as provide greater insight into the etiopathogenesis of MDD.

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11-C "Neural Correlates of Stress Susceptibility in the Ventral Hippocampus - Nucleus Accumbens Pathway"

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Epidemiological data indicates stress is a major risk factor for depression, yet not everyone reacts to stress the same way. Understanding the mechanisms underlying differential vulnerability is essential for targeted treatment and, ultimately, prevention. In previous work we identified that pre-existing differences in nucleus accumbens (NAc) activity associate with resilience to chronic social defeat stress (CSDS), an animal model for depression, indicating pre-stress neural activity may influence future susceptibility even in the absence of other identified risk factors. In this work, we investigated how the ventral hippocampus-nucleus accumbens pathway influences vulnerability to stress. Activation of this pathway has been shown to induce susceptibility *after* chronic stress in males, thus we hypothesized that increased activity *prior* to stress may predict increased depressive- and anxiety-like behavior following stress. Using fiber photometry, we recorded calcium transients in this pathway during standard tests of anxiety- and depressive-like behavior before and after chronic variable stress (CVS), a model for depression which is readily adaptable to males and females. We observed that individual differences in vHIP-NAc activity prior to stress predict post-stress behavior and that stress further modulates activity in this pathway.

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11-D "Densities and morphological properties of cortical vimentin- and GFAP-immunoreactive astrocytes in depressed suicides"

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Introduction: Post-mortem studies comparing brain samples from depressed suicides and matched controls have identified in the former group significant changes in the number, morphology and gene expression of astrocytes in regions implicated in mood regulation. All of the immunohistological studies, however, have used glial fibrillary acidic protein (GFAP) as an astrocyte marker. Here we carried out a comparative fine neuroanatomical analysis of astrocytes immunoreactive (-IR) for GFAP or vimentin (VIM) in the dorsolateral prefrontal cortex (BA8/9) from depressed suicides and psychiatrically healthy controls.

Methods: Frozen-fixed BA8/9 samples were provided by the Douglas-Bell Canada Brain Bank from 10 well-characterized depressed suicides and 10 matched healthy sudden-death controls were sectioned with a sliding microtome into serial 50µm-thick sections and immunostained for brightfield microscopy using primary anti-VIM (AbCam rabbit polyclonal antibody, ab92547) and anti-GFAP (AbCam chicken polyclonal, ab4674) antibodies. Stereological densities and morphometric properties of astrocytes were determined, respectively, using the optical fractionator method (*StereoInvestigator*) and by manual tracing (*Neurolucida*).

Results: We found a significant decrease in the number of VIM-IR astrocytes in both grey and white matter, as well as fewer primary processes and terminals in VIM-IR astrocytes in BA8/9 white matter from MDD samples.

Discussion: Combined with our preliminary data suggesting that VIM and GFAP label two mostly nonoverlapping astrocyte populations, these findings reveal that astrocytes labelled by multiple markers are affected in depression and suicide.

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12-A "Dcc Mutation Uncovers the Neural Circuits that Localise Pain in Mice"

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Nociceptive topognosis or the ability to localise noxious stimuli, is critical for avoidance of environmental dangers. Nociceptive information is carried from the periphery to different brain regions through spinal projection neurons (PNs). Mice with a spinal cordspecific knockout of Dcc, encoding a Netrin receptor, are unable to accurately localize noxious stimuli, similar to DCC mutant humans. However, the identity of PNs that transmit the location of a noxious stimulus to the brain remains unknown. To uncover it, I created DccPhox2a:Cre mice, in which the embryonic Phox2a:Cre driver deletes Dcc in a specific population of PNs. To assess nociceptive topognosis of DccPhox2a:Cre mice, thermal pain was induced by capsaicin injection into one of their hindpaws, and the accuracy with which they direct licking to the injection site was assessed. My results show that DccPhox2a:Cre mutants erroneously lick untreated limbs more frequently than control mice. Further behavioural analyses suggest that the function of local spinal nociceptive circuits is normal in DccPhxox2a:Cre mice arguing that their topognosis deficits uncover a function of Phox2a PNs in topognosis. More generally, my results provide a genetic inroad into discriminatory versus emotive organization of ascending nociceptive pathways.

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12-B "The Role of the Deubiquitinase USP2 in the Response of the Circadian Clock to Light"

Shashank Srikanta, Nicolas Cermakian

All aspects of human physiology are rhythmic with a period of approximately 24 hours. Disruption of these rhythms, called circadian rhythms, is a risk factor for various mental health disorders such as mood disorders. Hence, understanding mechanisms that can control circadian rhythms is of paramount importance. While extrinsically, light can affect these rhythms, intrinsically, circadian rhythms are controlled by tightly regulated transcription-translation feedback loops (TTFLs) and their post-translational modifications (PTMs). For example, ubiquitination and deubiquitination cycles are important PTMs, as they control the half-lives of the various players in the TTFL. USP2 is a deubiquitinase that is being studied in our lab, due to its involvement with many of the clock proteins. Our lab previously showed the importance of USP2 in the process of entrainment, i.e., the ability of the clock to adapt to external light cues. We now aim to elucidate the mechanisms involved in the regulation of clock entrainment by USP2, using a knock-out (KO) mouse model. We are delving further into this aspect using bioluminescence recordings of ex-vivo cultures of the Suprachiasmatic Nucleus (SCN, the site of the mammalian master clock) to understand the mechanisms of action of USP2 in the central clock. Having standardized the process of SCN culturing, we are now working towards treating SCN slices from *Usp2* WT and KO mice with glutamate, a proxy for light inputs to the SCN. Further, we are complementing these studies with mouse wheel-running locomotor activity recordings in light conditions such as the skeleton photoperiod and non-standard T-cycles, to understand the extent of involvement of USP2 to the process of entrainment. Our preliminary data from the skeleton photoperiod experiment show altered entrainability in KO mice, as compared to WT mice. This work will allow untangling of the mode of action of USP2 in the regulation of light entrainment of the central clock.

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12-C "Limited Bedding Stress Alters Adult Behaviour, Intestinal And Blood-Brain Barrier Integrity, And Microglial Homeostasis In Male And Female Mice"

J. Kasia Szyszkowicz, Iris Kim, & Giamal N. Luheshi

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Background: Early-life stress is an important risk factor for the development of psychiatric disorders – however, the mechanisms by which this vulnerability persists into adulthood remain largely unknown. We hypothesized that the psychiatric outcomes associated with early-life stress may induce an important shift in gut bacterial composition, that in turn promotes long-lasting changes in intestinal and blood-brain barrier integrity and disruptions in neuro-immune homeostasis.

Methods: C57Bl/6J mice were exposed to either a limited bedding stressor (reduced access to nesting material) or control (no change) condition between postnatal days(P)2 to P9. We assessed behaviour via novelty suppression of feeding, three-chamber social interaction and memory test, and elevated plus maze. Blood, brain, and gastrointestinal samples were collected at P60. We measured plasma cytokines (interleukin (IL)-1β, 6, 10, 17, and tumor necrosis factor(TNF)-α) by multiplex ELISA, mRNA expression of barrier integrity markers by qPCR, and microglial homeostasis in the CA1 and dentate gyrus using immunohistochemistry.

Results: Early-life stress altered social preference and memory (in males and females respectively) and had modest sex-specific effects on novelty supressed feeding and elevated plus maze. Although limited bedding did not alter plasma cytokine levels in adulthood, we noted a change in microglial density and distribution in in the dentate gyrus but not in the CA1. Finally, limited bedding reduced levels of claudin-5, a tight junction protein, in both the colon and the hypothalamus.

Conclusion: Collectively, these results support our hypothesis that the brain-immune-gut axis mediates the effects of early life stress into adulthood.

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12-D "A network perspective on the role of subcortical limbic system in chronic pain patient's clinical profile"

C. Tanguay-Sabourin & E. Vachon-Presseau

Background: Chronic pain, referred as a pain persisting past normal healing time, is considered a global health priority due to its worldwide prevalence and severe disability. Although the underlying etiology remains ambiguous, the limbic system circuitry has been found to play a determinant role in the risks for chronic pain (Vachon-Presseau, et al., 2016). However, the form in which this system relates to clinical pain observed in chronic patients is still elusive.

Objective: Here, we aim to observe the role of subcortical limbic volume in the patient's clinical pain profile using a network psychometric approach.

Method: This analysis was conducted on FMRI Software Library (FSL) version 6.0.1. We used FIRST, FSL's tool for automated subcortical segmentation derived from probabilistic atlas, to obtain subcortical volumes. This was done on the hippocampus, amygdala and nucleus accumbens, identified as the key limbic structures playing a role in chronic pain. From these volumes, we also regressed out the effect of gray-matter volume, gender, and age. These graymatter volumes were obtained using FAST, FMRIB Automated Segmentation Tool, to segment tissue type in T1w image. Prior scanning, participants reported their pain daily for two weeks using a visual analog scale, displayed on a cellphone app. From these Ecological Momentary Assessment (EMA), we obtained an average, a peak and a variability measure of their pain. Additional questionnaires and measures were taken on the day of scanning. This included pain duration, pain intensity (NRS), depressive mood (BDI-II), pain quality (MPQ), pain detection (painDETECT) and pain catastrophizing (PCS). Then, we derived a Gaussian graphical model from pairwise associations observed in the brain volumes and patient's clinical characteristics. This was done using an R software package, qgraph. While the network is undirected, the weights of the edges represent partial correlation coefficients (i.e controlling for the effect of all other variables). A regularization technique, the least absolute shrinkage and selection operator (LASSO) procedure, was used to conservatively identify only the relevant edges among the various pairwise associations estimated. Layouts for each network structure was computed using a force-displacement algorithm, placing nodes with strong connections centrally while leaving weakly connected nodes on the periphery. We also averaged each layout to allow proper visual comparison across models. The final accuracy of our model was evaluated visually by bootstrapping the edge weights' 95% CI using the package Bootnet.

Results: We found differential relations between subcortical limbic volumes and chronic pain patient's clinical characteristics. Associations between various clinical chronic pain features and subcortical volumes were attenuated after regularization, a substantial edge remains between the left amygdala and

averaged pain as well as the right nucleus accumbens and depressive mood.

Conclusion: This study suggests that adopting a network perspective may provide insights on how different brain components may target specific clinical characteristics in chronic pain patients.

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13-A "Neuropsychiatric symptoms are correlated with tau but not amyloid or neurodegeneration along the Alzheimer's disease spectrum"

Tissot, Cécile, BSc[1,2]; Pascoal, Tharick A. MD[1,2]; Therriault, Joseph, BSc[1,2]; Chamoun, Mira, PhD[1,2]; Lussier, Firoza[1,2]; Savard, Melissa, MSc[1,2]; Mathotaarachchi, Sulantha S., MSc[1,2]; Lessa Benedet, Andrea, MSc[1,2]; Thomas, Emilie M., PhD[1]; Parsons, Marlee, MD[1,2]; Rosa-Neto, Pedro, MD, PhD[1,2]; Gauthier, Serge, MD, FRCPC[1,3]

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Introduction: Neuropsychiatric Inventory-Questionnaire (NPI-Q) is a survey addressed to informants to assess the participant's neuropsychiatric symptoms (NPS) and their impact on the participant (global severity) and their informant (global distress). Thus, NPI-Q contains 2 global domains and 12 subscales: delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, motor disturbance, nighttime behavior and appetite. Although NPS has been closely related to the clinical progression to dementia1 in carriers of Alzheimer's disease (AD) pathophysiology, the relationship between NPS and brain amyloid and tau pathologies is still unclear. Here we hypothesize that tau and amyloid deposition as well as neurodegeneration associate with different subscales of the NPI-Q, across the AD clinical spectrum.

Methods: 94 individuals (CN = 74, MCI = 9, AD = 11) underwent positron emission tomography (PET) amyloid [^{18}F]AZD4694 and tau [^{18}F]MK-6240. [^{18}F]AZD4694 and [^{18}F]MK-6240 standardized uptake value ratios (SUVRs) used the cerebellum grey matter as the reference region and were calculated between 40-70 min and 90-110 min post-injection, respectively. A voxel based regression model2 evaluated the relationship between the accumulation of a biomarker, using [^{18}F]MK6240 or [^{18}F]AZD4694 PET scans, and the NPI-Q global scores, as well as the 12 subscales. The model's covariates were age, gender, years of education and diagnosis of participants.

Results: We did not find association between global NPI-Q scores (distress and severity) and brain amyloid deposition nor neurodegeneration. Tau deposition was however correlated with global NPI-Q severity and distress scores. Severity was associated with precuneus and frontal pole [^{18}F]MK6240 uptake; while distress correlated with precuneus, parietal association cortex, anterior cingulate, frontal and temporal lobe uptake. Additionally, [^{18}F]MK6240 uptake differed between the severity and distress scores in most domains, such as delusions, hallucinations, agitation, depression, anxiety, disinhibition, motor disturbance and appetite (Fig.2). The strongest correlations were found with depression, correlated with [^{18}F]MK6240 uptake in the frontal lobe and cuneus; hallucinations and delusions, showing high correlation with [^{18}F]MK6240 uptake in the cuneus;

motor disturbance in the supplementary motor area (SMA).

Conclusion: These preliminary results show a significant correlation between severity but more strongly with the distress caused by the patients' NPS in their caregiver and tau aggregation. The impacted regions for the global scores are known to be involved in self-consciousness and higher-order cognitive processes. They are also recognized as being associated with NPS and AD, and the subscales results show tau deposition in regions related to each symptom. This study demonstrates NPS correlate with tau only, and not amyloid or neurodegeneration, along the AD spectrum and it is thus important to assess them. Moreover, it emphasizes the importance of the informant's perspective in the management of the diseases, which is often overlooked. In effect, they seem to be able to perceive the first changes related to AD pathophysiologies.

References:

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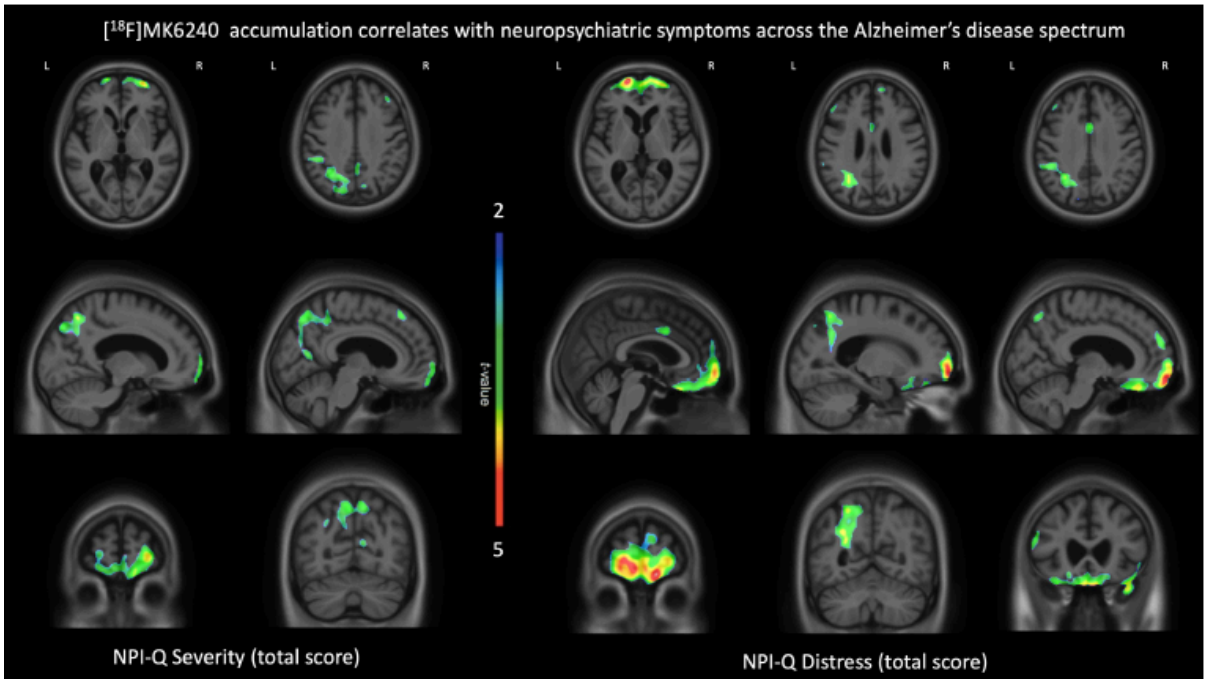

Figure 1: Parametric maps show significant correlation between Neuropsychiatric Inventory-Questionnaire (NPI-Q) severity and distress scores and [18F]MK6240.

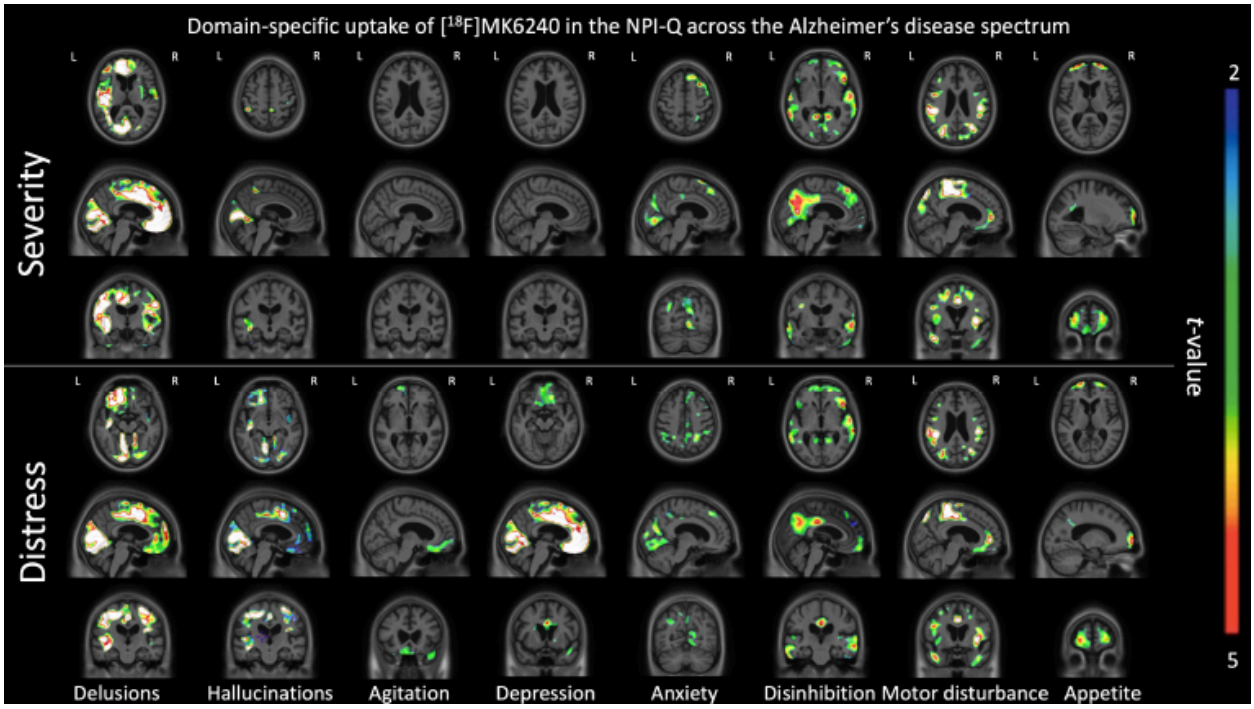

Figure 2: Parametric maps show significant correlation between domain-specific severity scores of the NPI-Q and [18F]MK6240.

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13-B "Characterization of Proteases Involved in Amyloid β Clearance"

Irem Ulku, Gerhard Multhaup

The canonical amyloidogenic pathway involves subsequent cleavage of the amyloid precursor protein (APP) first by β-secretase (BACE1) followed by γ-secretase to generate amyloid-β (Aβ) peptides of varying lengths. Among those peptides, Aβ42 is prone to aggregate and has toxic effects *in vitro* and *in vivo*. Recently, we have found a novel activity of BACE1, i.e. a BACE1-catalyzed cleavage of longer Aβ forms including Aβ40 and Aβ42, which results in the production of a non-amyloidogenic metastable intermediate, i.e. Aβ34. In contrast to Aβ42, Aβ34 is soluble, non-toxic and non-aggregating.

Aβ production involves two well-characterized proteases, β-secretase and γ-secretase, while Aβ clearance and degradation are mediated by numerous proteases with distinct characteristics, including sensitivity and specificity determined by pH and the respective subcellular localization. Pharmacological experiments suggest that Aβ peptides are degraded by a family of proteases collectively referred as Aβ-degrading enzymes (ADEs). However, specific proteases responsible for degradation of Aβ34 have not yet been identified or characterized in detail. Therefore, we aim to analyze proteases that are implicated in Aβ clearance and identify their potential role in Aβ34 degradation.

With regards to Aβ degradation, the most important difference among ADEs is their subcellular localization and their access to the Aβ pools. Aβ pools are defined according to subcellular localization; interstitial (extracellular), ER/golgi, endosomal, lysosomal and cytosolic. Endosomes and lysosomes are the sites where BACE1 is also located and active. Therefore, among ADEs, Endothelin Converting Enzymes (ECEs), Insulin Degrading Enzyme (IDE), Cathepsin B (Cat B) and Cathepsin D (Cat D), which have activity in either/both endosomes or/and lysosomes, are the prime candidates and of particular interest. Our preliminary data shows that in BACE1 overexpressing SH-SY5Y cells, Aβ34 levels increased upon ECE1 knockdown, which suggests a potential role for ECE1 in Aβ34 clearance. To further validate our results, transient transfection and overexpression of candidate proteases will be performed and the pattern of Aβ species and fragments thereof will be determined. A qualitative analysis using IP/MS analysis of cell media and lysates will reveal the Aβ species that are recognized as substrates by the proteases under investigation and the Aβ fragments that are generated upon the respective cleavage(s).

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13-C "Genetic analysis of Kirrel function in sensory neuronal map formation"

Neelima Vaddadi[1,2], Katrine Iversen[1,2], Reesha Raja[1,2], Alina Phen[1,3], Alexandra Brignal[1,3] ,Emilie Dumontier[1], Jean-François Cloutier[1,2,3]

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The establishment of neural maps during development requires the accurate targeting of axonal projections into spatially defined regions within the nervous system. The homophilic cell adhesion molecules Kirrel2 and Kirrel3 are differentially expressed in populations of neurons and have been proposed to regulate the targeting of axons by generating an axonal identity code of adhesion. Although mutations in the Kirrel3 genes have been identified in patients suffering from intellectual disability and autism, its function during neural map formation remains poorly understood.

We have evaluated the requirement for Kirrels 2 and 3 in neural map within the mouse olfactory system. We have shown that their differential expression in olfactory sensory neurons is critical for axonal targeting into synaptic units of the olfactory bulb, termed glomeruli. Furthermore, our analyses uncovered a neuronal sub-type specific role for Kirrels in olfactory sensory neuron axon within the olfactory bulb. To determine whether Kirrel homophilic adhesion is necessary for their function in axonal targeting, we have generated a mouse line expressing an adhesion-deficient form of Kirrel3 using Crispr-Cas9 genome editing. Our preliminary results indicate that preventing Kirrel3 adhesion leads to improper axonal coalescence within olfactory bulb glomeruli, indicating that Kirrel3 controls axonal targeting by mediating adhesion of axons with similar molecular identities. Our results shed new light on the function and molecular mechanism through which Kirrels contribute to the formation of neural maps. Future studies will be aimed at evaluating their function in synaptic development.

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13-D "Long-term optogenetic stimulation of Parvalbumin-positive interneurons at theta frequency (8 Hz) leads to paradoxical effects on ictogenesis"

Maxime Lévesque, Li-Yuan Chen, Guillaume Etter, Zahra Shiri, Siyan Wang*, Sylvain Williams and Massimo Avoli

*Presenting author

We aimed to establish the effects induced by long-term stimulation of parvalbumin-positive (PV) interneurons on seizures, interictal spikes and high-frequency oscillations (80-500 Hz) occurring after pilocarpine-induced *status epilepticus* (SE) – a model of mesial temporal lobe epilepsy (MTLE) - in transgenic mice expressing or not expressing ChR2. PV-ChR2 (n = 6) and PV-Cre (n = 6) mice were treated with pilocarpine to induce SE. Three hours after SE onset, unilateral optogenetic stimulation (450 nm, 50 mA, 20 ms pulses delivered at 8 Hz for 30 s every 2 min) of CA3 PV-positive interneurons was implemented for 14 continuous days in both groups. Results showed that rates of seizures ($p < 0.005$), interictal spikes ($p < 0.001$) and interictal spikes with fast ripples (250-500 Hz) ($p < 0.001$) were lower in PV-ChR2 than in PV-Cre mice. Ripples (80-200 Hz) occurring outside of interictal spikes had higher rates in the PV-ChR2 group ($p < 0.01$) while isolated fast ripples had lower rates ($p < 0.01$). However, seizure probability was higher during optogenetic stimulation in PV-ChR2 compared to PV-Cre animals ($p < 0.01$). Our findings show that the unilateral activation of CA3 PV-positive interneurons exert anti-ictogenic effects associated with decreased rates of interictal spikes and fast ripples in this MTLE model. However, PV-positive interneuron stimulation can paradoxically trigger seizures in epileptic animals, supporting the notion that GABAA signaling can also initiate ictogenesis.

This study was supported by the Canadian Institutes of Health Research (PJT153310 and MOP130328, M.A.; MOP119340, S.W.) and the Savoy Foundation (M.A.).

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14-A "Astrocytes in synaptic plasticity of pyramidal cells in layer 5 visual cortex"

Airi Watanabe, Per Jesper Sjöström

By enclosing pre- and postsynaptic compartments, astrocytes help form "tripartite" synapses. In this strategic position, astrocytes can bidirectionally communicate with neurons through the release of gliotransmitters – molecules synthesized or stored in glia cells that are able to be released and regulate physiological functions. Increasing evidence show astrocytic involvement in orchestrating synaptic plasticity which determines whether pre-existing connections between synapses strengthen or weaken and is a plausible mechanism for learning and memory formation. In acute slices, I visualized astrocytes in layer 5 of the developing mouse visual cortex using sulforhodamine 101 to target-patch a specific subset of SR101+ astrocytes and characterized their electrophysiological properties. I also investigated the possible role of a well-known gliotransmitter, D-Serine, on short-term pyramidal cell plasticity. This work provides a basis for understanding the properties of astrocytes in layer 5 visual cortex and explores a potential role for astrocytic regulation of neocortical plasticity in excitatory synapses. Future directions aim to elucidate the mechanisms of D-Serine-mediated downregulation of evoked release, and the role of astrocytes in long-term plasticity in the developing visual cortex

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14-B "ERP profiles for Chinese sentence processing: Relevant factors in noun-noun-verb structures with BA and BEI, and effects of adjective placement violations"

Wolpert M, Zhang H, Baum S, Steinhauer K

Mandarin Chinese and English both have poor inflectional morphology and canonical subject-verb-object word order, but are otherwise largely dissimilar languages. We took advantage of the cross-linguistic similarities and differences between the languages to conduct two EEG sentence processing experiments with Mandarin monolinguals in China, with the goal of confirming structural targets for a future study on English-Mandarin bilingualism and first language attrition in Canada.

In our first experiment, we investigated the effect of sentence structure and animacy on argument structure interpretation in noun-noun-verb (NNV) sentences. While English speakers rely on word order as their primary cue, Mandarin speakers give greater consideration to semantic knowledge to determine who did what to whom (Liu, Bates, & Li, 1992). For instance, the two sentences "the apple the boy eats" and "the boy the apple eats" are both grammatical and have the same meaning in Mandarin regardless of word order, namely that the boy eats the apple. Mandarin also has two coverbs, BA and BEI, which unambiguously assign undergoer and actor status, respectively, to their subsequent noun phrase. Participants' (n=39) EEG was recorded while reading NNV sentences with or without BA and BEI. After each sentence, participants indicated which noun they interpreted as the actor. Behavioral judgments showed main effects of structure and direction of semantic plausibility and a significant interaction between structure and semantic direction. We analyzed mean amplitude of ERPs at the verb at Cz and Pz electrodes from 300 to 500 ms, and preliminary results showed a greater N400 for the semantic anomalous compared to the semantic congruent condition for BA and marginally significant for BEI ($t(25)=2.0$, $p=0.06$) sentences. This contrasts slightly with Bornkessel-Schlesewsky et al. (2011), who investigated similar structures in spoken Chinese (with 25 native speakers of Mandarin in Germany) and found an N400 effect only for implausible BEI (but not BA) sentences; the observed N400 effect contrasts significantly with Chow & Phillips (2013), who reported P600 effects for Mandarin semantic reversals. These differences could be due to our participants being monolingual Mandarin speakers with very limited foreign language exposure or to experimental design differences (e.g., materials, task, or modality).

In our second experiment, we investigated Mandarin monolinguals' (n=32) processing of adjective-noun order violations. Because adjectives generally precede nouns in both English and Mandarin, we predicted that these structures would be resistant to language attrition, but it was unclear if violations in Chinese would elicit the same ERP effects as in English. Mean amplitude at Cz and Pz electrodes showed a greater N400 and P600 for sentences with adjective-noun

order violations, in line with results from English native speakers and Chinese learners of English (Steinhauer 2014). These data not only shed new light on Mandarin monolingual sentence processing, but also show promising targets for current efforts to study cross-linguistic influences in bilingual sentence processing and first language attrition.

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14-C "The role of mTORC2 in the spinal cord in the development of chronic pain"

Calvin Wong[1,2], Kevin Lister[1,2], Neil Wu[1], Shannon N. Tansley[1,2,3] , Sonali Uttam[1,2], Jieyi Yang[1], Alfredo Ribeiro-da-Silva[4,5], Arkady Khoutorsky[1,2,6,a]

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[a]Corresponding author

The development of pain is associated with the reorganization of spinal nociceptive circuits. 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: mTOR Complex 1 (mTORC1) and mTORC2. mTORC1 regulates the rate of mRNA translation. Much less is known about mTORC2, which has recently emerged as a key signalling molecule in a variety of cellular processes including synaptic plasticity.

Our experiments revealed an increase in p-AKT (S473), which is a proxy for increased mTORC2 activity, in the spinal cord in the model of inflammation-induced pain (Complete Freund's Adjuvant) and neuropathic pain (spared nerve injury). To study the role of mTORC2 in pain, we selectively ablated Rictor, a key protein within the mTORC2, in the dorsal horn of the lumbar spinal cord via intraspinal injection of AAV9- CMV-Cre into rictorfl/fl mice. Our behavioural experiments demonstrate that mice with reduced levels of Rictor in the spinal cord exhibit decreased hypersensitivity in a model of inflammatory pain. Conversely, intrathecal administration of the mTORC2 activator A-443654 induced prolonged mechanical hypersensitivity.

Our study shows for the first time that spinal mTORC2 is activated following peripheral tissue injury and demonstrates the central role of mTORC2 in spinal dorsal horn neurons in the development of pain hypersensitivity in response to inflammation.

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14-D "Re-balancing the eyes using monocularly-directed attention"

Sandy Wong, Alex Baldwin, Kathy Mullen, Robert Hess

Department of Ophthalmology, McGill Vision Research, McGill University

Although most people see the world binocularly, combining the visual scene from both eyes, we usually have one eye that is more dominant over the other. In some clinical conditions, when the vision in one eye is poor due to disease or dysfunction, the "good" eye may become very dominant and suppress the vision from the weaker eye. We think that, in some cases, this suppression may impair the recovery of the weaker eye. Hence, we are interested in understanding the mechanisms involved in eye dominance both for normal function and from the clinical perspective. Here we test whether attention directed to one eye only can influence the eye dominance, or balance between the eyes. This first project investigates this question in normal vision using a binocular rivalry task. Binocular rivalry is where visual perception alternates between different images presented to each eye, and the proportion of time an eye's image is perceived throughout a given duration reflects the strength of that eye's contribution to the visual percept.

We collected data from 22 adults with normal vision using four conditions where attention was directed to: 1) the left eye only, 2) the right eye only, 3) to both eyes, and 4) alternating between the left and right eye only. Incompatible grating stimuli were presented to the participants' two eyes. Throughout the task, participants used a joystick to continuously report which stimulus they saw, which was used as a measure of eye balance. Simultaneously, coloured circle stimuli were presented to either one or both eyes depending on the condition in order to direct attention to those eyes. Participants made judgements about the coloured circle stimuli in the high attention load condition and did not make judgements in the low attention load condition. To ensure that the changes in eye balance were not due to binocular rivalry itself, a control condition with only the binocular rivalry stimulus was used. No significant change in ocular dominance was found in this condition.

It appears that directing attention to one eye shifts eye balance such that it is more balanced. This effect is more significant when the weaker eye is cued (paired sample t-test, $P<0.05$). This result suggests that directed attention to one eye using a monocular cueing task has the potential to correct binocular imbalances.

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15-A "The effects of augmented feedback and its delivery schedule on motor learning of manual wheelchair propulsion technique in a virtual reality simulator"

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For new manual wheelchair (MWC) users, mastering safe and efficient propulsion technique is critical, as poor technique enhances risk for chronic pain and injury in the upper limbs. Specific propulsion training interventions are needed as the ideal propulsion technique is a complex novel skill that must be acquired through motor learning principles. Training using virtual reality simulators allows users to practice such tasks in a safe, controlled, and realistic environment. Augmented feedback (AF) may also be provided during simulator training to optimize motor learning. The purpose of this study is to investigate the effects of providing AF with various delivery schedules on motor learning of this complex skill, as well as to determine whether technique learned in a virtual environment transfer effectively to real-world propulsion. 30 healthy participants aged 18-35 will be randomly assigned to three groups. The high-frequency feedback group will receive AF for all propulsion during training. The faded feedback group will receive AF in a faded schedule. The control group will undergo the same training with no AF. Propulsion assessments will be performed at baseline in virtual (VE) and real environments (RE), 5 minutes after training in the VE, and 48 hours after training the VE and RE as retention and transfer assessments respectively. It is expected that those receiving AF will improve more from baseline to retention/transfer assessments than those in the control group. Furthermore, in accordance with the guidance hypothesis, it is also expected that this improvement will be more significant for the faded feedback group than the high-frequency feedback group. By examining the effects of AF and its delivery schedules, this study will provide valuable information for the design of low-cost propulsion training programs to help prevent the detrimental upper limb pain and injury that currently affects as many as 73% of MWC users.

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15-B "Hippocampal Input to the Nucleus Accumbens Shell Enhances Food Palatability"

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Background: Insight into the neural basis of hedonic processing has come from studies of food palatability in rodents. Pharmacological manipulations of the nucleus accumbens shell (NAcSh) have repeatedly been demonstrated to increase hedonic taste reactivity, yet the contribution of specific NAcSh circuit components is unknown.

Methods: Bidirectional optogenetic manipulations are targeted to the principal NAcSh projection neurons and afferent pathways of mice during free feeding assays. Number of licks per bout of consumption is used as a measure of food palatability, as it is confirmed to track sucrose concentration and subjective flavor preferences.

Results: Photoinhibition of NAcSh neurons, whether general or cell-type specific, is found to alter consumption without affecting its hedonic impact. Among the principal excitatory afferent pathways, we show that ventral hippocampal (vHipp) input alone enhances palatability upon low frequency photostimulation time-locked to consumption. This enhancement in palatability is independent of opioid signaling and not recapitulated by NAcSh or dopamine neuron photostimulation. We further demonstrate that vHipp input photostimulation is sufficient to condition a flavor preference, while its inhibition impedes sucrose-driven flavor preference conditioning.

Conclusions: These results demonstrate a novel contribution of vHipp-NAcSh pathway activity to palatability that may relate to its innervation of a particular region or neuronal ensemble in the NAcSh. These findings are consistent with the evidence that vHipp-NAcSh activity contributes to the pathophysiology of anhedonia and depression as well as the increasing appreciation of hippocampal involvement in people's food pleasantness ratings, hunger, and weight.

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15-C "Is Trauma-associated Sleep Disorder a Sub-form REM Sleep Behavior Disorder? A Canadian Longitudinal Study on Aging Cohort Study"

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Objective: To assess the differences between post traumatic stress disorder (PTSD)-associated sleep disorder (TSD), which may also trigger dream enactment during REM sleep, and possible idiopathic REM sleep behavior disorder (pRBD) in a 30,097-person national cohort.

Method: Participants, aged 45-85 years in Canada, were sampled by geographical density and recruited in the Canadian Longitudinal Study on Aging. Those self-reporting dementia or Parkinson's disease were excluded. Since TSD is commonly associated with PTSD, in the CLSA cohort, we defined TSD as dream enactment behavior among PTSD participants with nightmare/flashback symptoms. TSD was defined as:
1) Screen positive on Primary Care PTSD screen (PC-PTSD) questionnaire (cut-off ≥ 3),
2) Endorsing nightmares/recurrent thoughts of a traumatic experience
3) Screen positive on the RBD1Q
Results were compared to PTSD participants whithout TSD, and possible RBD patients without PTSD. A series of global health features, motor and sleep assessments, cognitive tasks and mental health variables were analysed cross-sectionally, adjusted by age and sex.

Results: 304 screened positive for TSD, 1,122 PTSD without TSD, and 857 with pRBD. TSD (56.58%; OR_{RBD}=1.82[1.39,2.38]) was more common among women. The mean of age was also slightly younger among the TSD (59±9) and the PTSD (60±9) than the pRBD (63±11). Compared to those with pRBD, TSD participants were more likely to report memory decline (9.24% vs. 1.73%, OR_{RBD}=6.09[3.2,12.27]), impairment in daily motor functions (1.20±1.56 vs. 0.60±1.08, OR_{RBD}=1.57[1.4,1.8]), and daytime sleepiness (26.1% vs. 11.7%, OR_{RBD}=3.0[2.1,4.3]) and endorse psychological distress (20.64±7.29 vs. 14.68±4.76, OR_{RBD}=3.08[2.04,4.61]). However, no difference in objective motor

performance was found in between TSD and pRBD; both TSD (28.83 seconds, OR_{RBD}=1.03[1.02,1.05]) and PTSD (27.33 seconds, OR_{RBD}=1.02[1.01,1.03]) participants showed slight psychomotor slowing than pRBD (27.07 seconds). TSD performed slightly poorer than the pRBD on the Stroop task (2.07 vs. 1.71, OR_{RBD}=1.09[1.03,1.15]).

Conclusion: Our study suggests that although TSD is relatively more similar to PTSD as a psychiatric disorder, it may share similar motor phenotype as pRBD.

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15-D "Transcriptional signatures of primary human microglia across the developmental time line at the single cell level"

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Microglia as the main resident immune cells of the central nervous system (CNS) have critical, underappreciated roles in development and in the maintenance of brain homeostasis. Microglia also become highly reactive throughout the course of all neurological disease including multiple sclerosis. To gain a clear insight regarding the role of microglia in CNS pathology we first need to understand the molecular mechanisms underlying development of these cells. Furthermore, it has been shown that animal model organisms consistently fail to mimic human physiological conditions. In the present study we isolate microglia from human surgical brain tissues from three different developmental timepoints including fetal, pediatric and adult. We investigate temporal changes in gene expression profiles and study heterogeneity within the microglia populations across the developmental trajectory using a single cell RNA-sequencing approach. Preliminary analysis shows that each time point has its own specific expression profile, with fetal and pediatric samples being more similar as compared to the adult population. HSPA1A, APOC1 and HLA-DPA1 are the most up regulated genes in fetal, pediatric and adult samples. In addition, the list of transcription factors (TFs) which control expression of genes have been identified in each time point. We also analyze the expression profiles of microglia isolated from human spinal cord autopsy samples which reveals unique transcriptional signatures of brain and spinal cord microglia. Microglia are implicated in the pathogenesis of most neurodegenerative and neuroimmunological diseases. Understanding the exact molecular mechanisms which underlie their development will likely provide insights into the pivotal roles these cells in normal brain development and disease.

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