



EARLY LIFE & PRENATAL HEALTH IN NEURODEVELOPMENT

Montreal

March 22-24, 2023

McGill - Douglas
Max Planck Institute
of Psychiatry



Adversity
& Mental Health



Full abstracts with all authors, references, and figures can be found at:
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About

ELePHiNt

ELePHiNt 2023 aims to bring together an international community of researchers who study the impact of prenatal and early life on neurodevelopment in an intimate, forward-thinking event against the backdrop of breathtaking Montreal. The conference will feature catalyzing keynotes, inspiring short talks, and plenty of time for in-depths discussion.

Organizing committee

Amalie Couch	Lani Cupo	Rugile Matuleviciute
Melissa Bauman	Mallar Chakravarty	Anthony Vernon

Schedule

TS: Trainee Speaker, KL: Keynote Lecture.

Wednesday, 22 of March

13:00–14:00	Registration		
14:00–14:20	Welcome remarks		
14:20–16:00	TS	Trainee Talks Session 1	See List Below
16:00–17:00	KL	Naguib Mechawar McGill University	Longterm impact of child abuse on cortical plasticity
17:00	Cocktail Evening at Local Bar		

Thursday, 23 of March

9:00–10:40	TS	Trainee Talks Session 2	See List Below
10:40–11:00	Coffee		
11:00–12:00	KL	Amanda Kentner Massachusetts College of Pharmacy and Health Sciences	Rescue effects of enrichment on early life inflammation
12:00–13:00	Catered Lunch		
13:00–14:40	TS	Trainee Talks Session 3	See List Below
14:40–15:00	Coffee		
15:00–16:00	KL	Liisa Galea CAMH and University of Toronto	Sex differences in neuroscience
16:00–17:00	Structured Discussion		
17:00	Dinner (reservation required)		

Friday, 24 of March

9:00-10:40	TS	Trainee Talks Session 4	See List Below
10:40-11:00		Coffee	
11:00-12:00	KL	Yi Zuo UC Santa Cruz	Chronic stress and cortical synaptic circuits
12:00-13:00		Catered Lunch	
13:00-14:40	TS	Trainee Talks Session 5	See List Below
14:40-15:00		Coffee	
15:00-16:00	KL	Anthony Vernon King's College London	Pro-inflammatory cytokines in neuron-microglia interactions
16:00-16:45		Structured Discussion	
16:45-17:00		Closing statements	

Order of Participants

Wednesday, March 22		
Day	Anticipated start	Participant Name
Wednesday	14:20	Alice Morgunova
Wednesday	14:45	Candice Canonne
Wednesday	15:10	Rugile Matuleviciute
Wednesday	15:35	Michel Rafael Garcia Miranda
Keynote, 16:00-17:00 Naguib Mechawar		
Thursday, March 23		
Thursday	9:00	Kelly Perlman
Thursday	9:25	Sowmya Narayan
Thursday	9:50	Samuel Richer
Thursday	10:15	Xinyuan Li
Keynote, 11:00-12:00 Amanda Kentner		
Thursday	13:00	Karen Dominguez - Cancino
Thursday	13:25	Lizette Herrera
Thursday	13:50	Katherine Séguin
Thursday	14:15	Kristelle Alunni - Menichini
Keynote, 15:00-16:00 Liisa Galea		
Friday, March 24		
Day	Anticipated start	Participant Name
Friday	9:00	Amanda Keller
Friday	9:25	Tanya Capolicchio
Friday	9:50	Pablo Martínez
Friday	10:15	Daphne Nakhid
Keynote, 11:00-12:00 Yi Zuo		
Friday	13:00	Chelsea Kelland
Friday	13:25	Tara Delorme

Friday	13:50	Raphaëlle Giac
Friday	14:15	Simone Grant
Keynote, 15:00-16:00 Anthony Vernon		

List of Abstracts – Talks

Wednesday 22nd, 2023

Afternoon Trainee Talks

MicroRNA expression profiles from peripheral blood serve as biomarkers for depression risk in children and adolescents

Alice Morgunova, Nicholas O'Toole, Carine Parent, Corina Nagy, Gustavo Turecki, Patricia Pelufo Silveira, Anthony Gifuni, Tiffany Ho, Ian Gotlib, Michael Meaney, Cecilia Flores

TS

McGill University, Montreal, Canada

Background: Discovering objective molecular markers of psychiatric risk, particularly complemented with longitudinal clinical records, will aid with early disease diagnosis. Emerging role of microRNAs (miRNAs) in neurodevelopment and mental illness warrants a non-invasive investigation focused on early life. In this study we conducted a high-throughput analysis of miRNA profiles of peripheral fluids derived from blood in cohorts of children and adolescents with or without clinical levels of depression. Methods: A total of 170 blood plasma samples from the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) and dried blood spots samples from an older cohort, the Teen Inflammation Glutamate Emotion Research (TIGER; N=62), were sequenced using small RNA protocol. Trimmed reads were processed following exceRpt small RNA-Seq pipeline, differential expression done using DESeq2 package, gene ontology and disease associations with MetaCore. GUSTO: categorical groups were assigned according to Child Depression Inventory (CDI) score measures over two time points (age 8-10 yr); including threshold based high and low CDI score groups. TIGER groups were assigned based on the diagnosis and Reynolds Adolescent Depression Scale (RADS). Results: We identified miRNAs differentially expressed (DE) between males and females, and between children with high vs low CDI scores in the GUSTO cohort ($p_{adj} < 0.05$). Some DE miRNAs were specific to the stability of depression score. Target genes of DE miRNAs were associated with neurodevelopment and pain disease. In TIGER, DE miRNAs were identified between (i) MDD vs Controls, (ii) subjects above or below a RADS cutoff threshold, and (iii) adolescents with high and low suicidal ideation threshold. Conclusions: We identified key circulating miRNAs linked to early depression onset. The nature of our study population allows us to probe into ongoing neurodevelopmental processes that may shape lifelong vulnerability to disease.

Characterizing Von Economo Neurons in Schizophrenia and Major Depressive Disorder

Candice Canonne, Anaïs Aghaby-Cloutier, Florence Mechawar, Claudia Belliveau, Maria Antonietta Davoli, Lena Palaniyappan, Naguib Mechawar

TS

McGill University, Montreal, Canada

Von Economo neurons (VENs) are a type of bipolar spindle-shaped neurons found in some regions in the human brain including the anterior cingulate cortex (ACC) and frontal insula (FI). These neurons, absent in rodents, have been described in a few other species with large brains and complex social structures, and associated with guilt, trust, empathy and formation of social bonds, among others. Studies are increasingly implicating VENs in brain disorders: an alteration in the number and morphology of VENs has been reported in alcoholism, autism spectrum disorder (ASD), schizophrenia (SCZ), behavioral variant frontotemporal dementia (bvFTD) and suicide in psychosis. Recently, a transcriptomic analysis of VENs enabled the identification of differentially expressed genes in VENs vs pyramidal neurons, in particular a higher expression of genes associated with psychiatric disorders, namely, SCZ, depression and substance abuse. However, the involvement of VENs in neuropsychiatric disorders remains to be largely characterized. In my project, I aim to identify the specific VENs features associated with major depressive disorder (MDD) and SCZ. I hypothesize that VEN densities, morphologies, and transcriptomic profiles are altered in mental illness, and that these alterations display illness-specific differences. The densities of VENs in the FI and ACC of well-characterized post-mortem brain samples are analyzed at a 20x magnification using QuPath. The density of pyramidal cells is also determined in order to evaluate whether any significant difference is due to VENs specifically or, more generally, to layer Vb neurons. Optimized protocols will be presented with the first dataset on the comparison between VEN densities in samples from MDD vs matched control samples. These results will provide a better understanding of the cellular changes that occur in MDD and SCZ and should shed new light on the possible implication of VENs in mental illness.

Microglia heterogeneity: how diverse are transcript isoforms?

Rugile Matuleviciute, Rosemary Bamford, Johnathan Mill, Deepak Srivastava, Anthony Vernon

TS

King's College London, London, United Kingdom

Although microglia are functionally and transcriptionally heterogeneous, little is known about transcript diversity in these cells and how transcript isoforms are selected. Differential isoform expression could in part be regulated via RNA modification N6-methyladenosine (m6A) as m6A is involved in alternative splicing (Adhikari et al., 2016) among other functions. Deciphering microglia isoform landscape could help to identify therapeutic targets in disease conditions. We differentiated four control human induced pluripotent stem cell (hiPSC) lines into microglia-like (MGL) cells and neural progenitor cells (NPCs). RNA from hiPSCs, day 0, 1 and 14 for MGLs, and day 7, 12, 19, and 26 for NPCs was used for qPCR to confirm cell identity and determine m6A machinery expression patterns. With Oxford Nanopore Technologies (ONT) ultradeep targeted transcriptome sequencing, we profiled isoform diversity across development using samples from day 1 and 14 microglia from six control and three 22q11del hiPSC lines. cDNA was enriched across a panel of > 300 genes associated with development and neurodevelopmental disorders. cDNA was sequenced on ONT PromethION flow cells and analysed using a bespoke data analysis pipeline developed by our group for isoform visualization and quantification (Leung et al., 2021). We first identified the pattern of m6A machinery expression in the NPCs and microglia. We then detected both common and novel transcript isoforms expressed in microglia during development. We also explored which of the isoforms are timepoint-and-sex-specific. To assess whether the microglial transcript landscape differed based on the disease state, we compared the transcript isoforms between the control and 22q11del samples. Identifying different transcript isoforms in developing microglia helps to better understand what contributes to transcriptional diversity of these cells. To investigate whether choice of transcript isoforms is influenced by RNA methylation, we are establishing inducible hiPSC knockdown lines of m6A machinery.

Sexual differentiation of the limbic system during puberty: a scMultiomics approach

Michel Rafael Garcia Miranda, J. Ding, Carina Nagy.

TS

McGill University, Montreal, Canada

Major depressive disorder (MDD) represents a worldwide social and economic burden, nonetheless, the burden is not distributed equally, females are twice as likely as males to suffer from MDD. This difference in prevalence is maintained across different cultures while considering a possible help-seeking bias. Pointing to a biological cause, namely, the sexual differentiation of the limbic system. The mammalian brain is sexually differentiated during the perinatal period by the action of sex hormones, establishing sex-typical neural circuitry and modulating sex-specific behaviors during adulthood. Recent works point towards puberty as a period of further sexual differentiation in response to sex hormones. This period is of particular interest since the sex differences in the incidence of MDD only arise after the beginning of puberty. Methods: We will conduct a longitudinal study that explores how gene expression evolves in regions of the limbic system of mice across 21 time points comprising peri-puberty, puberty, and adulthood in both sexes. We will isolate the nucleus accumbens, ventral hippocampus, and prelimbic cortex through precision brain punches. We will perform RNA-seq in these regions and analyze how gene expression diverges across both sexes. At the time points with the most significant changes, we will perform single-cell analysis of paired RNA-seq and ATAC-seq data to better understand the trajectory of different cell types in these regions throughout puberty. Initial analyses will be done using Seurat for the transcriptomic data and Signac for the chromatin conformational changes identified from the ATAC protocol. Further, we will assess the relationship of systemic and central levels of sex hormones between and cell and region-specific gene expression changes. Blood will be collected, and serum separated at the time of sacrifice. The serum and brain regions' sex hormones levels will be measured by ELISA tests.

Afternoon Keynote

Naguib Mechawar

KL

McGill University, Montreal, Canada

Dr. Mechawar's presentation will focus on recent post-mortem data generated in well-characterized human brain samples showing that child abuse has lasting consequences on major features associated with cortical plasticity, namely myelination and perineuronal nets.

Thursday 23rd, 2023

Morning Trainee Talks

Phospholipid fatty acid composition of the uncinata fasciculus: a study of child abuse and age

Kelly Perlman, Chuck T. Chen, Raphaël Chouinard-Watkins, Mackenzie Smith, Arnaud Tanti, Massimiliano Orri, Gustavo Turecki, Richard P Bazinet, Naguib Mechawar

TS

McGill University, Montreal, Canada

Introduction: Child abuse (CA) is the primary preventable risk factor for the development of mental illness. Severe CA has been specifically linked with long lasting disruptions of oligodendrocyte and myelin function. The myelin sheath is highly enriched in lipids and CA-related myelin findings may represent alterations of its lipid profile, especially given that the composition of fatty acids (FA) in myelin phospholipids influence its compactness, stability, and permeability. Notably, there is a paucity of information on FA composition in cortical white matter (WM) compared to long-range fiber bundles. Therefore, the objective of this study is to quantify FA concentrations in the post-mortem human uncinata fasciculus (UF), a major association white matter tract, and characterize the relationships with CA and age. Methods: FA concentrations in all major phospholipid pools were compared between depressed suicides with a history of CA, depressed suicides without CA, and non-psychiatric controls. Group-matched brain samples were provided by the Douglas-Bell Canada Brain Bank. Total lipids were extracted according to the Folch method, lipids were separated into respective classes using thin-layer chromatography, and FA methyl esters from each fraction were quantified using gas chromatography. Results: Phospholipid fractions revealed divergent patterns of FA composition with respect to CA and show differences as compared to cortical white matter. Across the phospholipid classes, the age relationships vary quite significantly, though there is some overlap, for example with C22:4n-6 (adrenic acid) and other polyunsaturates. Conclusion: We present the first ever characterization of UF phospholipid fatty acids and describe their relationships with CA and age. These data will be supplemented with cholesterol quantification as well as myelin ultrastructure metrics in order to more comprehensively understand their biological relevance.

Combining prenatal and postnatal stressors to characterize long-term effects of developmental stress exposure in a mouse model

Sowmya Narayan, Joeri Bordes, Lucas Miranda, Micha Czisch, Tibor Stark, Stoyo Karamihalev, Simone Roeh, Elisabeth Binder, Mathias V Schmidt

TS

Max Planck Institute for Psychiatry, Munich, Germany

Early life adversity and prenatal stress are established risk factors for developing psychiatric disorders in young adulthood. The biological basis of how early exposure carries into adulthood and manifests as susceptibility is not yet fully understood, and we therefore aim to characterize it using a mouse model. Our focuses are 1) whether exposure to both stressors would lead to an adaptive or maladaptive response in adulthood (2-hit hypothesis), 2) highlighting critical sex differences, and 3) translatability of our mouse model. We exposed mice to either prenatal stress (PNS) of maternal CORT injections during late pregnancy, early life stress (ELS) of limited bedding and nesting in the first week of life, or a combination (PN+ELS), and used behavioral paradigms with robust readouts harnessing deep learning-based technology to assess social, anxiety-like and depression-like behaviors. We collected tissue from 10 brain subregions implicated in stress for bulk RNA sequencing, assessed resting state brain activity via meMRI, and neural circuit activation with cFos expression. Behavioral testing in early adulthood revealed higher prevalence of anxiety and depressive-like behavior and social subordination. These phenotypes are present at a more elevated degree in combined treatment PN+ELS mice than PNS-only or ELS-only mice. Currently physiological characterization is under way, and preliminary results find differences in resting state brain activity of PN+ELS animals. As this combination of stress treatments in the mouse is translationally relevant to stress exposure during the human neurodevelopmental period, we intend to use this model to study the transcriptional response to stress across brain regions moving forward. We intend to further translational validity by overlapping our mouse RNAseq dataset with that of a human post-mortem MDD cohort, and then focus on further dissecting the roles of specific molecular signatures that are conserved across species.

Social stress in adolescence induces ectopic growth of mesolimbic dopamine axons to the prefrontal cortex

Samuel Richer, Andrea H. Pantoja Urban, Aoran Song, Sehar Gul, Giovanni Hernandez, Cecilia Flores

TS

McGill University, Montreal, Canada

Bullying in adolescence can hamper prefrontal cortex (PFC) development, impairing its role in controlling impulse behavior and negatively affecting psychopathology onset and severity. In adolescence, dopamine (DA) axons expressing the guidance cue receptor DCC undergo targeting events in the nucleus accumbens (NAcc), forming enduring synaptic connections. However, mesocortical DA axons continue to grow from the NAcc to the PFC over adolescence remaining vulnerable to experiences. Using an accelerated social defeat stress model for adolescent male mice (AcSD), we showed that social stress downregulates DCC receptors in DA neurons leading to altered PFC DA connectivity and inhibitory control deficits in adulthood (Vassilev et al., 2021; 2022). In this study, we tested if AcSD induces the mistargeting of NAcc DA axons and their ectopic growth to the PFC. To track adolescent PFC DA axon growth, we unilaterally microinjected a retrogradely transported virus expressing floxed Flp recombinase into the NAcc of postnatal day 21, DATCre male C57BL/6J mice. Simultaneously, we microinjected into the ipsilateral ventral tegmental area a Flp-dependent enhanced yellow fluorescent protein (eYFP) virus. Flp recombinase is therefore only expressed in Cre⁺ DA neurons that have reached the NAcc by early adolescence. At postnatal day 25, mice were exposed to AcSD or to control conditions. In adulthood, PFC DA axon growth was assessed by quantifying eYFP⁺ terminals with stereology. Males exposed to AcSD in adolescence show a greater number of eYFP⁺ axons in the adult PFC compared to controls, indicating ectopic innervation of NAcc DA axons in the PFC. DA axons are the only axons known to grow during adolescence. Here we show that social defeat stress during this critical maturational period induces targeting errors and rerouting of NAcc DA axons to the PFC. This effect is likely mediated by DCC downregulation in DA axons and may be the cause of immature impulse control in adulthood.

Effects of disaster-related prenatal maternal stress on default mode network structural connectivity in young adults: Project Ice Storm

Xinyuan Li, Xiangyu Long, Suzanne King, Catherine Lebel

TS

McGill University, Montreal, Canada

The default mode network (DMN) plays a crucial role in cognition, decision-making, and emotion regulation. Studies show that prenatal depression alters the functional organization of the DMN in children. However, it is unknown whether these alterations persist beyond childhood. Examining a natural disaster as the source of prenatal maternal stress, we aimed to determine whether the timing of stress exposure moderates DMN structural connectivity in young adults. Ice storms struck Quebec in January 1998. We recruited women who were within 3 months of conception or who were pregnant during the ice storm and measured their objective hardship. At 19 years, their young adult offspring underwent diffusion MRI. Graph theory analysis was used to examine DMN organization as it related to prenatal objective hardship controlling for parental socioeconomic status and child sex. Moderation analyses were implemented with bootstrapping of 20,000 resamplings to examine the moderating effect of exposure timing. Significant interactions of timing of exposure and objective hardship were found on global efficiency, nodal degree centrality and characteristic path length of the DMN. When stress exposure occurred during preconception and the first month of pregnancy, higher hardship was significantly related to lower global efficiency, lower nodal degree centrality and higher characteristic path length; when exposure occurred during the third trimester of pregnancy, there was a trend that higher hardship was related to higher global efficiency, higher nodal degree centrality and lower characteristic path length. The results suggest the long-lasting effects of prenatal maternal stress, and highlight preconception and the first month of pregnancy as vulnerable windows for prenatal stress weakening DMN structural connectivity.

Morning Keynote

Amanda Kentner

KL

Massachusetts College of Pharmacy and Health Sciences

In Dr. Kentner's work, her lab uses animal models of early-life inflammation to explore the potential for environmental enrichment to offer protection and remediation against associated cognitive and behavioral (primarily social) detriments. During this talk, she will share some of her animal models and show how they characterize the specific enrichment components and neuroendocrine mechanisms that underlie the benefits of enhanced environments.

Challenges for developing interprofessional collaboration between health professionals working with pregnant women exposed to cannabis

Karen Aileen Dominguez Cancino, Kristelle Alunni-Menichini, Pablo Alberto Martinez Diaz, Rose Chabot, Yolaine Frossard de Saugy, Karine Bertrand, Nadia Lespérance, Julie Loslier, José Ignacio Nazif-Munoz

TS

Université de Sherbrooke, Sherbrooke, Canada

Canadian Federal and provincial governments have made explicit efforts to inform and tackle health risks associated with cannabis consumption during pregnancy, especially since the Cannabis Act in 2018. Nonetheless, studies had shown that health professionals could have a different approach regarding cannabis consumption. The heterogeneity of these approaches when interacting with pregnant women could thus recreate ambiguities towards cannabis use. A coordinated and aligned response from health care is needed. In this way, interprofessional collaboration may respond successfully to the needs of women exposed to cannabis during pregnancy. The study aims to identify how interprofessional collaboration unfolds when attending pregnant women exposed to cannabis. As part of a mixed-methods study, we will be conducting focus groups and interviews with health professionals (physicians, nurses, psychologists, midwives, and social workers) working in Québec's health system in person or virtually. A thematic content analysis will be performed with the data available by the end of February 2023. We will present a preliminary synthesis of different narratives of health professionals regarding how interprofessional collaboration unfolds in the context of pregnant women exposed to cannabis. We will consider their approaches in attention to their interactions with other health professionals within Quebec's health system when attending pregnant women. Conclusion. Identifying how interprofessional collaboration unfolds can allow the recognition and subsequent interventions to develop an interprofessional response to meet the needs of pregnant women with cannabis use in the health system more comprehensively.

Chronic variable stress induces sex-specific depressive-like behavioral and brain changes in mice

Lizette Herrera, Daniel Gallino, Rosemary C. Bagot and M. Mallar Chakravarty

TS

McGill University, Montreal, Canada

Stress is a major risk factor for depression. Chronic variable stress (CVS), an animal model for depression, reveals important sex-differences in stress susceptibility (females respond to shorter periods of stress). However the majority of animal studies include only males. Here, eight-week old C57BL/6 female and male mice were left undisturbed or exposed to 6- or 28-days of CVS, respectively (1hr daily stressor: 100 foot shocks, tail suspension or restraint; n=10M/9F control, 10M/10F CVS). Longitudinal magnetic resonance imaging and behavioral testing (anxiety-like behavior: open field test; social withdrawal: social preference test) were acquired at baseline and 24-hours after the last stressor. Using a multivariate analysis, we identified shared and sex-specific phenotypes of neuroanatomical changes associated with depressive- and anxiety-like behavior. In females, 6-days of CVS were sufficient to capture significant neuroanatomical remodeling that covaried with anxiety-like behavior and social withdrawal. Whereas in males, neuroanatomical alterations were associated only with anxiety-like behavior.

Maternal mental health and difficult child temperament: the mediating role of postpartum sleep quality

Katherine Séguin, Giac, R, Gingras, M., Booij, L., Lippé, S., Vaillancourt, C., Herba, C. and the RESPPA team

TS

Université du Québec à Montréal, Montreal, Canada

Since the pandemic started, prevalence rates of depression and anxiety in pregnant women have been reported to be higher than pre-pandemic levels. This is of concern since such prenatal symptoms have been associated with poorer child development. Maternal sleep quality may play a role in the relation between mothers' prenatal symptoms and child socio-emotional development. Yet, associations between maternal mental health, sleep quality, and child temperament are relatively unexplored. We aimed to examine associations between maternal symptoms of anxiety, depression, and stress in late pregnancy and child temperament in the context of the COVID-19 pandemic, and whether maternal postpartum sleep quality mediates associations. Methods: From October 2020-July 2022, pregnant women were recruited across Quebec (www.resppa.ca). Prenatal anxiety, depression, and stress symptoms were measured via GAD-7, Edinburgh Postnatal Depression Scale, and Perceived Stress Scale. At three months postpartum, mothers reported on their sleep quality via the Pittsburgh Sleep Quality Index and the perception of their child's temperament via the Infant Characteristics Questionnaire. Linear regressions, including mediation tests, were performed with SPSS-Process (N=363). Maternal symptoms in the 3rd trimester were associated with worse postpartum sleep quality (anxiety: $\beta = .233$, $p < .001$; depression: $\beta = .218$, $p < .001$; stress: $\beta = .221$, $p < .001$) and with difficult temperament ($\beta = .143$, $p = .007$; $\beta = .196$, $p < .001$; $\beta = .185$, $p < .001$). There was a partial indirect effect between maternal depression and stress, respectively and temperament via postpartum sleep quality ($\beta = .138$, $p = .010$; $\beta = .123$, $p < .023$). The direct link with temperament was no longer significant ($\beta = .078$, $p = .144$) after considering sleep suggesting a total indirect effect for anxiety. Postpartum sleep quality may be an important intervention target for improving maternal well-being and promoting child development.

How Pregnant Women Assess Their Cannabis Use Since Legalization Through the Lens of Intersectionality: Preliminary Results

Kristelle Alunni-Menichini, Pablo Alberto Martinez Diaz, Karen Aileen Dominguez Cancino, Rose Chabot, Yolaine Frossard de Saugy, Nadia L'Espérance, Karine Bertrand, Julie Loslier, José Ignacio Nazif-Munoz

TS

McGill University, Montreal, Canada

Cannabis is the most used substance during pregnancy, along with alcohol, for multiple reasons, such as to tackle physical and mental issues or to replace other substances perceived as more dangerous. Although knowledge about the effects of cannabis on the unborn child is still limited, we do know that cannabis crosses the placenta and that this can lead to adverse childhood consequences (e.g., lower birth weight, neurodevelopmental and emotional alterations). Considering this, multiple questions have emerged since the legalization of cannabis in Canada. Among others, little is known about the effect of cannabis legalization on pregnant women's choices to continue using cannabis or not, and the stigma they face. One of our objectives is to understand, from an intersectional perspective, how pregnant women assess their cannabis use. As part of a mixed-methods study, we use a qualitative design to reach our objective. One-hour individual interviews are being conducted in person or virtually and sociodemographic questionnaires are going filled. A thematic content analysis is being performed with the support of NVivo. Through the lens of intersectionality, we will present preliminary results associated with their choice concerning their cannabis use (e.g., stop, suspend, continue, increase during their pregnancy). More precisely, we will present them in a way that better understand the contribution of individual (e.g., age, socioeconomic status, traumas), relational (e.g., within their partners) and systemic aspects (e.g., intersecting stigmas, cannabis legalization) in their choice. These results will allow us to better understand how different aspects of pregnant women's lives, including the legalization of cannabis, may have influenced their assessment of cannabis use, and to explore how to reduce stigma they face and enhance their empowerment. More broadly, this study will help a deeper understanding of cannabis use among pregnant women in Quebec.

Afternoon Keynote

Liisa Galea

KL

Treliving Family Chair in Women's Mental Health, CAMH and University of Toronto, Canada

Sex differences exist in many neurological and neuropsychiatric diseases in prevalence and manifestation of disease. Given these differences it is vital researchers consider sex and gender effects in neuroscience. Dr. Galea will outline the many types of sex differences, some common biases in neuroscience, and how we can use the power of sex differences to unravel the many mysteries of the brain.

Friday 24th, 2023

Morning Trainee Talks

Genetic anxiety for substance abuse transmission in substance abusing mothers

Amanda Keller, Emily Bosk, and Michael MacKenzie

TS

McGill University, Montreal, Canada

A growing body of research has explored genetic risk factors associated with the development of substance use disorders (SUD) (Bevilacqua and Goldman, 2009). Yet the science behind the etiology for SUDs is complex and multi-factorial. There is also limited research on how parents with a SUD understand the risk of transmission of SUD to their children. This study examines how parents of young children with SUD make meaning of their children's risk for addiction, adding important insight into potential areas for intervention. Data from this study is drawn from a larger project examining treatment for caregivers with SUD and their young children ages zero to five being served by three child and family serving agencies in the United States. Twenty-nine in-depth, semi-structured Working Model of the Child Interviews (WMCI). WMCI interviews were qualitatively analyzed using content analysis, to examine maternal concerns related to intergenerational risk for the development of SUDs in their children. Data analysis reveals that 29% of mothers reported that they had "addiction genes", "the gene", or "bad genes" and they had concerns that their children inherited this "gene". A few mothers reported that they believed their children were destined to inherit their addiction. Findings suggest that among mothers with SUD, a subset experiences considerable anxiety about their children's future risk for developing a SUD. This anxiety represent a misunderstanding about the science of human genetics. While biological and disease models of addictions have served to reduce stigma and remove blame from individuals, these practice frameworks may have the unintended consequence of heightening parental anxiety that they may have passed a genetic predisposition to their child.

Tetrahydrocannabinol in adolescence disrupts dopamine-associated guidance cues and the development of inhibitory control in a sex-specific manner

Tanya Capolicchio, Giovanni Hernandez, Katherina Estrada, Emilie Dube, Cecilia Flores

TS

McGill University, Montreal, Canada

Dopamine (DA) axons continue to grow to the prefrontal cortex (PFC) in adolescence, fine-tuning impulse control. This is mediated the guidance cue receptor DCC. Adolescent exposure to 5mg/kg of tetrahydrocannabinol (THC; a dose reaching plasma levels comparable to those seen in moderate use in humans) alters *Dcc* mRNA expression in DA neurons in a sex-specific manner in mice. The microRNA miR-218 appears to be an epigenetic regulator of these changes, but only in males. Here we investigated if these molecular alterations associate with sex-dependent changes in adult impulsivity. Adolescent male and female C57/Bl6 mice received 5 non-contingent i.p. injections of THC (5 mg/kg) or vehicle, once every other day. In adulthood mice underwent Go/No-Go testing to quantify inhibitory control. Adult males administered THC in adolescence have less commission errors than controls, indicating improved action control, but show more premature responses, indicating impaired waiting impulsivity. THC in adolescence does not alter adult impulsivity in females. Our results suggest that moderate THC exposure in adolescence alters adult inhibitory control in a sex- and impulsivity domain-specific manner. These changes may result from disruption in PFC DA development induced by changes in the DCC guidance cue system.

Challenges in using administrative health databases for perinatal mental health research in Quebec

Pablo Alberto Martinez Diaz, Kristelle Alunni-Menichini, Karen Aileen Dominguez Cancino, Rose Chabot, Yolaine Frossard de Saugy, Karine Bertrand, Nadia L'Esperance, Julie Loslier, Helen-Maria Vasiliadis, Christophe Huynh, José Ignacio Nazif-Munoz

TS

Université de Sherbrooke, Sherbrooke, Canada

In Quebec, events such as the legalization of cannabis (a public policy) and the COVID-19 pandemic (an external shock) have occurred in recent years, and their associations with perinatal mental health (PMH) outcomes at the population level need to be understood. For instance, little is known about how cannabis legalization may modify substance use or substance-related disorders during the perinatal period. Additionally, preliminary evidence suggests that PMH - particularly among women - has been significantly affected by the COVID-19 pandemic. Exploiting administrative health databases (AHD) holds tremendous potential for public health research and concerted action, allowing, for instance, the assessment of PMH outcomes at the population level in different territories over time. The Institut national de santé publique du Québec (INSPQ) has AHD available for use. However, the exploitation of these AHD involves challenges such as building a partnership between researchers and the INSPQ, supervised access to AHD, the use of a combination of codes from the International Classification of Diseases and Procedure Codes to identify pregnant women and obtain data on PMH outcomes, and the use of statistical procedures to protect the confidentiality of small amounts of data, among others. This talk will address these challenges focusing on the study of PMH in Quebec from the experience of a group of researchers who have had access to the INSPQ's SISMACQ medical-administrative database. The background to this experience is a mixed-methods study aimed at understanding how cannabis use among pregnant women in Quebec has evolved with attention to their individual and partners' behaviors, health system factors, and cannabis policies. We hope this talk will provide attendees with valuable insights into the potential and challenges of using AHD for perinatal mental health research in Quebec.

Limbic subfields associated with mental health symptoms in youth with and without prenatal alcohol exposure

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TS

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Prenatal alcohol exposure (PAE) can result in reduced brain volumes in limbic structures associated with mental health. We tested whether hippocampal, amygdala, or thalamus subfields were associated with depression or anxiety symptoms in youth with and without PAE. 34 children with PAE and 72 unexposed controls aged 7-16 years (10.7 ± 2.2 , 62M/44F) completed a T1-weighted MRI. FreeSurfer 7.1.1 was used to segment hippocampal, amygdala, and thalamic subfields (Iglesias et al., 2015; Saygin et al., 2017; Iglesias et al., 2018). Mental health symptoms were measured using the Behavioural Assessment System for Children caregiver report (Reynolds et al., 2011). ANCOVAs examined group differences in subfield volumes and associations between Anxiety and Depression subscales and volumes, with group, group-brain interactions, age, and gender. 14 hippocampal and 12 thalamic subfields were smaller in the PAE group than controls (all $p \leq .05$). There were no group volume differences in the amygdala. Depression symptoms were negatively associated with right central lateral, laterodorsal, and lateral posterior thalamic nuclei volumes in the PAE group only ($p=.018$; $p=.003$; $p=.003$). Left central nucleus volume was negatively associated with depression symptoms and the hippocampal amygdala transition area was negatively associated with anxiety symptoms in the unexposed group but not in the PAE group ($p=.029$; $p=.047$). Anxiety was negatively associated with 5 thalamic and 13 amygdala subfields (all $p \leq .05$) across groups. There were no associations between hippocampal subfield volumes and depression symptoms. Youth with PAE have smaller hippocampal and thalamic subfields than unexposed controls, as well as different associations between volume and internalizing symptoms. Depressive symptoms and limbic brain structure differs in those with and without PAE. Smaller subfields are associated with more anxiety symptoms in youth.

Morning Keynote

Yi Zuo

KL

University of California, Santa Cruz, USA

Dr. Zuo's talk will focus on the impact of chronic stress on cortical synaptic circuits in the mouse, and strategies to prevent or rescue such detrimental effects.

Characterizing the impact of maternal immune activation on the development and function of the offspring's immune system

Chelsea Kelland, Ana-Maria Iosif, Apurv Srivastav, Melissa D Bauman, Judy Van de Water 

University of California, Davis, USA

Activation of the maternal immune system during pregnancy is an environmental risk factor for a plethora of neurodevelopmental disorders such as autism spectrum disorder and schizophrenia. To date, studies have found that MIA induces neuropathological and behavioral abnormalities in adult offspring. Little is known about the impact MIA has on the development and function of the offspring's immune system. To assess immune development and response in offspring following maternal immune perturbation, we performed a longitudinal study of maternal immune activation (MIA) in the nonhuman primate model via polyinosinic:polycytidilic acid (PolyI:CLC). Specifically, twenty-four pregnant rhesus macaques were given three injections of PolyI:CLC or saline. To confirm MIA, cytokine levels in plasma isolated from dam peripheral blood obtained 6-hours post final PolyI:CLC injection were measured. The offspring were then surveyed from birth with blood collected at postnatal day (PND) 30, PND 90, PND 180, 1yr, 2yr, 2.5yr, 3yr, 3.5yr, and 4yr. Similarly, plasma these timepoints was used to measure cytokine expression. Moreover, offspring cognition and behavior was investigated for future correlation analyses. PolyI:CLC injection during early gestation altered maternal cytokine profiles with increased expression of the antiviral cytokines such as IFN- γ , IL-12/23, IL-15, and IL-18 as well as cytokines associated with anti-inflammatory and TH2 responses in the MIA dams compared to the saline controls. Further, longitudinal analysis of MIA offspring profiles revealed persistent changes in the expression various cytokines associated with innate and adaptive immune responses as compared to saline offspring. Our data shows that MIA during early gestation has a long-term impact on immune development and function in offspring, suggesting the presence of a between maternal immune perturbation during gestation and immune system imprinting in the offspring.

Sex differences in behavioural, cellular, and molecular responses to circadian disruption and prenatal immune activation in mice

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TS

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Most individuals with neurodevelopmental disorders (NDD) experience sleep/circadian rhythm disruptions. Exposure to prenatal infection increases the risk of developing NDD. We studied how circadian disruption contributes to NDD using the Maternal Immune Activation (MIA) protocol in mice, which models prenatal infection. NDD result from exposure to multiple risk factors, thus we explored if MIA combined with circadian disruption during adolescence (critical period of brain development) would synergistically induce sex-specific deficits in offspring. We injected pregnant dams with the viral mimic poly IC (or saline; SAL) at embryonic day 9.5. Between postnatal weeks 3-7, we subjected offspring to constant light (LL) which induces circadian disruption or standard light:dark cycles (LD). Behavior was tested, microglia were imaged, and gene expression was measured in offspring. We observed group x lighting interactions mainly in males when assessing behaviors related to cognition, anxiety, and sociability. For example, in males, MIA induced social deficits, whereas the combined effects of MIA and LL-exposure diminished these deficits. As well, hippocampal microglial morphology was significantly altered. MIA in males (not females) caused a more activated microglial profile, while LL-exposure induced a less reactive profile and less dense distribution of microglia. Finally, we explored hippocampal gene expression. MIA led to many differentially expressed genes in males, which was greatly diminished in the MIA+LL group. We also identified transcriptional synchrony between groups within sexes, and discordant patterns between sexes. We are analyzing significant clusters of co-expressed genes affected by MIA and LL. The individual and combined effects of MIA and LL are sex-specific. MIA mainly affected males on behavioral, cellular, and molecular levels, and in many cases, the addition of LL diminished those effects.

COVID-19-related concerns and mental health among pregnant women and new mothers

Raphaëlle Giac, Marie-Pier Gingras, Katherine Séguin, Linda Booij, Sarah Lippé, Cathy Vaillancourt, Catherine Herba and the RESPPA team

TS

Université du Québec à Montréal, Montreal, Canada

The COVID-19 pandemic has been linked to increased levels of distress among expectant and new mothers, who may be especially concerned about the perceived risk and transmission of the virus during the perinatal period and the health of their baby. We examined whether a self-reported positive test for COVID-19 might be associated with COVID-19-related concerns about infection and symptoms of stress, depression, general anxiety, and pregnancy anxiety among pregnant women and new mothers. Preliminary analyses were performed in a subgroup ($n=732$) of the RESPPA cohort. Participants completed online questionnaires at each pregnancy trimester (T1, T2, T3) and at 3 months postpartum (T4). COVID-19-related concerns about infection, transmission and health were measured using 6 questions (Cronbach alpha range: 0.85-0.87). Symptoms of stress, depression, general anxiety and pregnancy anxiety were measured via the PSS, EPDS, GAD-7 and PRAQ. Data were analysed using independent sample t-tests. At T4, mothers who reported having received a positive COVID-19 test ($n=122$) indicated fewer COVID-19-related concerns ($M=2.91$, $SD=1.52$) compared to those who reported they had not tested positive ($n=571$) ($M=3.53$, $SD=1.49$), $t(691) = 4.129$, $p < .001$. Women who prenatally reported (T1, T2, or T3) testing positive for COVID-19 had depression symptoms at T4 ($M=5.69$, $SD=4.35$) that were marginally significantly lower than the ones who did not report testing positive ($M=7.12$, $SD=5.12$), $t(513) = 1.865$, $p = .063$. No other significant differences emerged for stress, general anxiety, and pregnancy anxiety ($p > .5$). Those who reported testing positive for COVID-19 reported fewer COVID-19-related concerns and tended to report fewer depression symptoms postnatally (T4). Future studies could investigate whether the COVID-19-related concerns experienced during the pregnancy have a longer-term impact on the mental health of these women.

MIA offspring characterization: neuroinflammation, neuroarchitecture changes, or both?

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TS

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Women exposed to infections during pregnancy have an increased risk of having a child with a neurodevelopmental disorder (NDD). The maternal immune response has been identified as a risk factor for NDDs using preclinical maternal immune activation (MIA) models. While these models have been helpful in elucidating phenotypes that MIA causes, the underlying neurobiology remains poorly understood. Does MIA create persistent neuroinflammation and cell death that correlate with behavioral phenotypes? Or could the behavioral changes be due to differences in the cytoarchitecture of the brain established during neurodevelopment? We treated time-mated Sprague Dawley rats with several dosages (0, 50, and 100 $\mu\text{g}/\text{kg}$) of LPS to stimulate the maternal immune system at GD14.5. Following behavioral characterization of the offspring, we micro dissected the medial prefrontal cortex and amygdala to examine levels of pro-inflammatory cytokines and Nuclear factor- κB (NF κB). In a separate cohort of MIA and control offspring, we carried out an exploratory study using cortical in vitro culture to assess cellular composition and neuronal development using a tri-culture (neurons, astrocytes and microglia) model. We predict that rat MIA offspring may show an increase in neural inflammation in adulthood, which correlates with behavioral changes. MIA cortical cultures will also likely show deviations neuronal development, astrocyte and microglia number. Conclusions: This data will allow us to understand the underlying mechanisms that may affect neurodevelopment in a rat MIA model.

Afternoon Keynote

Anthony Vernon

KL

King's College London

Dr. Vernon will discuss the role of IFN- γ and IL-6 signalling in molecular and cellular phenotypes associated with neurodevelopmental disorders using human stem cell models of neuron-microglia interactions

Enablers and barriers to effective parenting within the first 1000 days in low socio-economic communities of South Africa

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* Abstract accepted, speaker unable to present

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The first 1000 days is the period between conception and a child's second birthday. Globally, research on parenting is in an advanced stage, but parenting research focusing specifically on parenting in this developmental phase is limited in South Africa. Therefore, this study explores the enablers and barriers to effective parenting within the first 1000 days through the lens of parents and caregivers in low socio-economic communities. This study was conducted in low socio-economic communities of South Africa. An exploratory qualitative research design explored the enablers and barriers to effective parenting within the first 1000 days of life. Thirty participants were purposively selected and interviewed in this study. A semi-structured interview schedule was used for all interviews. The data were analysed using inductive thematic analysis. Two main categories emerged (effective parenting enablers and effective parenting barriers) during the data analysis. The main enablers of effective parenting within the first 1000 days of life include a support system, healthy behaviours/environment, job opportunities, religion, information/knowledge, and professional assistance. On the other hand, the main barriers to effective parenting were low socio-economic circumstances, environmental circumstances, lack of partner's support, the negative impact of technology, and lack of access to services. Enablers that need to be promoted for effective parenting range from support systems to professional assistance for parents. Also, barriers that need to be removed for effective parenting range from low socio-economic circumstances to a lack of partner's support for parents. This is because effective parenting is vital in improving developmental outcomes for children within the first 1000 days of life. Therefore, there is a need to develop policies and interventions to promote effective parenting within the first 1000 days in the communities.