# CCNP ANNUAL MEETING 2023
# Program Overview
# Faculty Club, University of Toronto
# Toronto, Ontario
# September 21 - 23

## *Acknowledgments*

In keeping with CMA guidelines, program content and selection of speakers are the responsibility of the planning committee. Support is directed toward the costs and not to individual speakers through an unrestricted educational grant.

The Canadian College of Neuropsychopharmacology highly appreciates the support of the following sponsors:

**Otsuka/Lundbeck Canada Pharmaceutical Inc.** for their ongoing sponsorship of the Heinz Lehman, the Innovations in Neuropsychopharmacology and the Young Investigator Awards.


**Boehringer-Ingelheim** for sponsoring this year's annual meeting.

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## Presidential Welcome

Since 1978, Canadian neuroscientists, psychiatrists, and their trainees have been gathering annually at the Canadian College of Neuropsychopharmacology meeting to exchange groundbreaking discoveries in basic and clinical research.

Finally, after two consecutive virtual meetings, the 2023 annual conference of the Canadian College of Neuropsychopharmacology is back in person. This year the meeting is in Toronto – a multicultural and cosmopolitan city renowned for its many centers involved in brain sciences and recognized as an international hub of arts and culture.

This meeting has been made possible thanks to the effort of the Local Organizing Committee comprised of Dr. Daniel Mueller (Chair), Mahavir Agarwal, Amer Burhan, Shaheen Darani, Melissa Perreault, Joshua Rosenblat, Caleb Browne, Crystal Clark, Benoit Mulsant, and Lena Quilty. As has been the case for many annual CCNP meetings, the professional assistance of Ms. Rachelle Anderson has been invaluable in the organization of this year's conference. On behalf of the CCNP Executive and the Council, I wish to thank her for her constant help and effort to maintain the college's functioning.

The main goal of the 2023 meeting is to provide a venue for Canadian scientists conducting research in neuropsychopharmacology to meet once again in person and to discuss timely and important issues in the field of neuropsychopharmacology. The scientific program showcases basic and clinical scientists and emphasizes translational approaches in topics including substance use disorders, neurodevelopment, and therapeutics. We are pleased to have as our Keynote speaker Dr. David Nutt (Imperial College London) who has become a leader in Psychedelic Psychiatry. The program also features a career panel by Dr. Shaheen Darani (University of Toronto) to discuss issues related to career development. The 2023 scientific program includes women, underrepresented minorities, and early career scientists/clinicians, exemplifying the commitment of CCNP to diversity and inclusion.

CCNP congratulates the winners of the W.G. Dewhurst awards and the six trainees selected to present their work in the Next Generation Symposium.

I look forward to welcoming you in Toronto and I hope that you will join us to make the 2023 CCNP annual meeting an enriching and unforgettable learning experience.

Sincerely,

Cecilia Flores, Ph.D.

President, CCNP

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## *OVERVIEW OF EVENTS*

**All sessions will be at the Faculty Club, 41 Willcocks Street, Toronto, ON**

**THURSDAY, SEPTEMBER 21, 2023**

1800 – 21:00 Welcome Reception, "Prenup Pub" second floor, 191 College Street, Toronto https://www.prenuppub.com/

**FRIDAY, SEPTEMBER 22, 2023**

08:00 – 17:00 Registration

08:00 – 08:45 Breakfast (Main Lounge)

08:45 – 09:00 Welcoming Remarks (Wedgewood Room)
**Dr. Cecilia Flores – CCNP President** (McGill University)

09:00 – 10:00 **Panel 1: Cell-Specific Mechanisms in the Response to Stress and Rapidly Acting Antidepressants** (Wedgewood Room)
**Chair: Dr. Natalina Salmaso** (Carleton University)

09:00 – 09:20 **Dr. Argel Aguilar-Valles** (Carleton University)
*Translational mechanisms of ketamine's antidepressant effects in rodents*

09:20 – 09:40 **Dr. Marie-Eve Tremblay** (University of Victoria)
*Microglial modulation using gamma oscillations to promote synaptic plasticity and mediate fast-acting antidepressant effect: from ketamine to light flickering entrainment*

09:40 – 10:00 **Dr. Natalina Salmaso** (Carleton University)
*Chronic stress decreases astroglial functions related to neuronal plasticity in the mPFC*

10:00 – 10:30 **Next Generation Symposium I** (Wedgewood Room)
**Chair: Dr. Argel Aguilar-Valles** (Carleton University)

10:00 – 10:15 **Jana Totzek** (McGill University)
*Longitudinal inference of hippocampal volume and morphometric hippocampal-cortical connectivity in psychotic disorders*

10:15 – 10:30 **Jonathan Lieberman** (McMaster University)
*A tale of two targets: differential effects of posterior cingulate cortex- and amygdala-targeted neurofeedback on posttraumatic stress disorder (PTSD)-related neural activation*

10:30 – 10:45 Break (Main Lounge)

10:45 – 11:45 **Panel 2: Unraveling the Intersectionality of Binge Eating and Addictive Disorders** (Wedgewood Room)
**Chair: Ms. Sarah Brassard** (McMaster University)

10:45 – 11:05 **Dr. Katia Belfort** (University of Strasbourg, France)
*Sucrose bingeing in mice alters reward-related behaviors and neuroinflammatory processes*

11:05 – 11:25 **Dr. Sarah E. Racine** (McGill University)
*Examining stress-induced changes in "wanting" and "liking" of palatable food in women with binge eating*

11:25 – 11:45 **Dr. Lindsay Bodell** (University of Western Ontario)
*Examining neural responses to anticipating or receiving monetary rewards and the development of binge eating in youth*

11:45 – 12:00 Break and lunch (Main Lounge)

12:00 – 13:00 **Keynote Speaker: Dr. David Nutt (virtual presentation via Zoom)**
(Wedgewood Room)
(Imperial College London)
*Psychedelic psychiatry – past, present and future*

13:00 – 13:15 Break (Main Lounge)

13:15 – 14:15 **Next Generation Symposium II** (Wedgewood Room)
**Chair: Dr. Daniel Mueller** (University of Toronto)

13:15 – 13:30 **Fatema El-Sayegh** (Carleton University)
*Inactivation of Cnot3 elicits sex-specific alterations in behaviours relevant for autism spectrum disorders*

13:30 – 13:45 **Alysha Sultan** (University of Toronto)
*Correlates of cannabis use disorder and cannabis use among adolescents with bipolar disorder and major depressive disorder in the National Comorbidity Survey-Adolescent Supplement (NCS-A)*

13:45 – 14:00 **Blake Noyes** (Queen's University)
*Eye movement measures may identify potential biomarkers for adolescent depression*

14:00 – 14:15 **Mariel Lepra** (University of Toronto)
*Translocator protein distribution volume, a positron emission tomography marker of gliosis in anorexia nervosa*

14:15 – 15:00 **Career Panel: Oh the Places You Will Go: Faculty Development and Mentorship to Support Career Success** (Wedgewood Room)
**Dr. Shaheen Darani** (University of Toronto)

15:00 – 16:00 Poster Session I (Room 201 and 205)

16:00 – 16:15 Remove / Setup of posters

16:15 – 17:15 Poster Session II (Room 201 and 205)

18:30 Banquet (Faculty Club)

**SATURDAY, SEPTEMBER 23, 2023**

07:30 – 10:00 Registration

08:00 – 08:45 Breakfast (Main Lounge)

08:45 – 09:00 Welcoming Remarks (Wedgewood Room)

09:00 – 10:00 **Panel 3: Neural Mechanisms of Early Life Stress as a Psychiatric Risk Factor** (Wedgewood Room)
**Chair: Dr. Maithe Arruda-Carvalho** (University of Toronto Scarborough)

09:00 – 09:20 **Dr. Maithe Arruda-Carvalho** (University of Toronto Scarborough)
*Synaptic maturation of prefrontal cortex pathways modulating emotional learning and stress sensitivity*

09:20 – 09:40 **Dr. Cecilia Flores** (McGill University)
*Decoding the impact of social stress in adolescence on the maturing prefrontal cortex*

09:40 – 10:00 **Dr. Derya Sargin** (University of Calgary)
*The long-term impact of early life stress on serotonin circuits and behaviour*

10:00 – 10:15 Break (Main Lounge)

10:15 – 11:15 **Panel 4: Novel Therapeutics for Treatment-Resistant Depression** (Wedgewood Room)

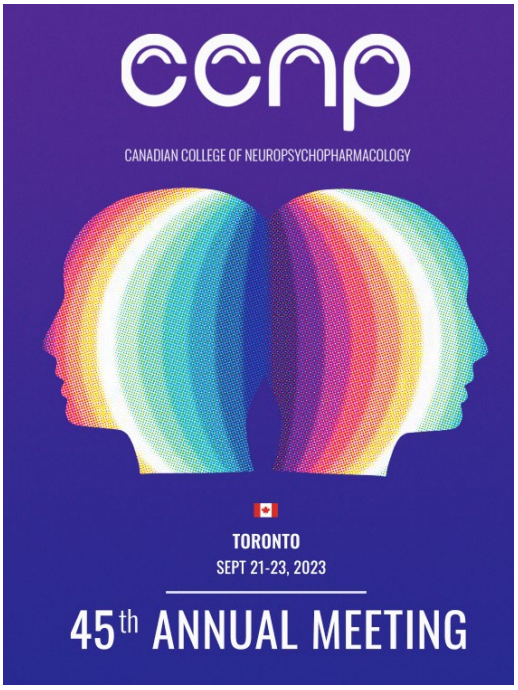
**Chair: Dr. Mikaela Dimick** (University of Toronto)

10:15 – 10:35 **Dr. Mikaela Dimick** (University of Toronto)
*Nitrous oxide treatment for bipolar depression: cerebrovascular mechanisms*

10:35 – 10:55 **Dr. Joshua Rosenblat** (University of Toronto)
*Ketamine and psilocybin for treatment-resistant mood disorders*

10:55 – 11:15 **Dr. Alexander McGirr** (University of Calgary)
*Pharmacologically enhanced transcranial magnetic stimulation for major depressive disorder: safety of extended dosing with D-Cycloserine as an adjunct to intermittent theta-burst stimulation*

11:15 – 11:45 Closing Remarks (Wedgewood Room)
**Dr. Cecilia Flores – CCNP President** (McGill University)



*Friday, September 22, 2023*
*Abstracts for Oral Presentations*

**Panel 1: Cell-Specific Mechanisms in the Response to Stress and Rapidly Acting Antidepressants**

**Translational mechanisms of ketamine's antidepressant effects in rodents**
Dr. Argel Aguilar-Valles, Carleton University

Ketamine is a rapidly acting antidepressant recently approved for treatment-resistant major depressive disorder. Ketamine stimulates the mammalian target of rapamycin complex 1 (mTORC1) pathway, leading to the activation of mRNA translation initiation, neuronal plasticity and behavioural responses. We have explored the neuronal substrates of this effect, uncovering different contributions of the mTORC1 pathway in different neuronal populations.

**Microglial modulation using gamma oscillations to promote synaptic plasticity and mediate fast-acting antidepressant effect: from ketamine to light flickering entrainment**
Dr. Marie-Eve Tremblay, University of Victoria

Light flickering stimulation provides a non-invasive approach to boost gamma waves (30–100 Hz), a well-characterized effect of ketamine, and promotes brain remodeling through microglia. In this talk, I will describe ketamine and light flickering stimulation (at 40 and 60 Hz) actions on microglial structure and function, and their association with synaptic plasticity outcomes. Altogether, our data will help to pave the way for a novel strategy to promote synaptic plasticity through microglial modulation.

**Chronic stress decreases astroglial functions related to neuronal plasticity in the mPFC**
Dr. Natalina Salmaso, Carleton University

A number of astroglial functions modulate local neuronal plasticity including the production of synaptogenic cues that are integral to synaptic plasticity and the donation of astroglial-specific components to perineuronal nets; mesh like structures that surround cortical interneurons that inhibit neuronal plasticity. In this talk I will draw upon our astroglial cell-specific sequencing and single cell sequencing studies to bring together glia and neurons into a cellular systems-level understanding of the effects of chronic stress on neuroplasticity.

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**CCNP Next Generation Symposium 1**

**Longitudinal Inference of Hippocampal Volume and Morphometric Hippocampal-Cortical Connectivity in Psychotic Disorders**
Jana F. Totzek, MSc [1,2], M. Mallar Chakravarty, PhD [1,2,3], Ridha Joober, MD, PhD [1,2], Ashok Malla, MD, FRCPC [1,2], Jai L. Shah, MD, FRCPC [1,2], Alexandra L. Young, PhD [4], Martin Lepage, PhD [1,2] & Katie M. Lavigne, PhD [1,2,5] Affiliations [1] Department of Psychiatry, McGill University, Montreal, Quebec, Canada [2] Douglas Research Centre, Montreal, Quebec, Canada [3] Department of Biological and Biomedical Engineering, McGill University, Montreal, Quebec,

Canada [4] Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom [5] Montreal Neurological Institute and Hospital, McGill University, Montreal, Quebec, Canada

Introduction: Hippocampal volume and hippocampal-cortical connectivity are significantly reduced in psychosis. Yet, the temporal order in which these two deteriorate across subtypes of psychosis remains to be determined. To this end, we implemented SuStaIn, a machine-learning algorithm which uniquely combines disease progression modeling and clustering. Methods: We sampled cross-sectional data from 175 patients with psychosis and 117 non-clinical controls from two datasets on first- and multi-episode psychosis. 18 hippocampal volumes were extracted through the MAGeT-algorithm and CIVET-derived cortical thickness values were parcellated into 62 DKT-regions. Structural covariances and then subject-specific structural covariance matrices were extracted for patients and controls by the means of the Jackknife Bias Estimation procedure. Hippocampal-cortical connectivity was then derived through the graph-theoretical participation coefficient after grouping the 18 hippocampal regions into a hippocampal module and estimating the inter-modular connectivity with the 7 Yeo networks. SuStaIn was implemented across three separate analyses. The first analysis combined 8 measures of (bilateral white matter and subfield) volume and connectivity, while two follow-up analyses examined the 18 volumes and 18 participation coefficients separately. Results: Following 10-fold cross-validation, SuStaIn revealed two subtypes in which either deteriorated white matter or subfield volume preceded deteriorations in hippocampal-cortical connectivity. The follow-up analyses showed that reductions in subfield volume preceded either no further deteriorations in connectivity, deteriorations of the input regions or across broad regions of the hippocampus. Reductions in white matter volume were followed by connectivity deteriorations in either the left hemisphere, in input regions or broadly across the hippocampus. Conclusions: These findings show that hippocampal volume deteriorates prior to morphometric hippocampal-cortical connectivity. Further, a deterioration of subfield volume can but does not need to evoke deteriorations in connectivity, while a deterioration of white matter volume necessarily does. These findings provide distinguishable neural pathways which might underlie the heterogeneous clinical presentation of psychotic disorders.

**A Tale of Two Targets: Differential Effects of Posterior Cingulate Cortex- and Amygdala-targeted Neurofeedback on Posttraumatic stress disorder (PTSD)-related Neural Activation**

Jonathan M. Lieberman[1,2] | Daniela Rabellino[2,3] | Maria Densmore[2,7] | Paul A. Frewen[3,4] | David Steyrl[5] | Frank Scharnowski[5] | Jean Théberge[2,6,7,8] | Richard W.J. Neufeld[3,4,7,9] | Christian Schmahl[10] | Rakesh Jetly[11] Benicio Frey[1] | Tomas Ros[12] | *Ruth A. Lanius[2,3,7] | *Andrew A. Nicholson[1,5,6,11,12,13] [1]Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada, [2]Imaging, Lawson Health Research Institute, London, Ontario, Canada, [3]Department of Neuroscience, Western University, London, Ontario, Canada, [4]Department of Psychology, Western University, London, Ontario, Canada, [5]Department of Cognition, Emotion, and Methods in Psychology, University of Vienna, Vienna, Austria, 6Department of Medical Biophysics, Western University, London, Ontario, Canada, 7Department of Psychiatry, Western University, London, Ontario, Canada, 8Department of Diagnostic Imaging, St. Joseph's Healthcare, London, Ontario, Canada, 9Department of Psychology, University of British Columbia, Okanagan, Kelowna, British Columbia, Canada, [10]Department of Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health Mannheim, Heidelberg University, Heidelberg, Germany, [11]The Institute of Mental Health Research, University of Ottawa, Royal Ottawa Hospital, Ontario, Canada, [12]Department of Neuroscience and Psychiatry, University of Geneva, Geneva, Switzerland, [13]Atlas Institute for Veterans and Families, Ottawa, Ontario, Canada

Introduction: Using fMRI-based neurofeedback (fMRI-NFB), individuals learn to self-regulate brain function associated with neuropsychiatric symptoms, including PTSD. In clinical studies, selecting the specific brain region for neurofeedback-mediated regulation is primarily informed by the neurobiological characteristics of the participant population and desired clinical outcomes. There is a strong link between PTSD symptoms and multiple functional disruptions in the brain, including hyperactivity within both the amygdala and posterior cingulate cortex (PCC). As such, several previous fMRI-NFB studies have trained individuals with PTSD to downregulate activity within each of these brain regions. However, the differential effect of neurofeedback target selection on clinical outcomes and PTSD-related neural activation has not previously been investigated.
Methods: We compared the whole-brain activation of individuals with PTSD between two fMRI-NFB studies downregulating either amygdala (n = 14) or PCC (n = 14) activity. Additionally, we assessed the change in PTSD symptoms over the course of neurofeedback training between participants in each of these two studies.
Results: For participants receiving PCC-targeted neurofeedback, as compared to amygdala-targeted neurofeedback, we observed decreases in neural activity across the brain including in several regions that are critically implicated in PTSD psychopathology (i.e., bilateral cuneus/calcarine cortex, left superior parietal lobule/angular gyrus, left occipital pole, and right superior temporal gyrus). Conversely, for participants receiving amygdala-targeted neurofeedback, as compared to PCC-targeted neurofeedback, we did not observe any differential whole-brain activity between groups. As a critical control, participants did not differ in their ability to downregulate the target brain region. Importantly, amygdala-targeted neurofeedback did not lead to improved PTSD symptoms, whereas PCC-targeted neurofeedback was associated with reduced reliving and distress symptoms. Conclusion: Taken together, neurofeedback-mediated regulation of the PCC, as opposed to the amygdala, appears to be differentially associated with reductions in PTSD symptoms and normalized PTSD-associated alterations in brain activity during a single training session.

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**Panel 2: Unraveling the Intersectionality of Binge Eating and Addictive Disorders**

**Sucrose bingeing in mice alters reward-related behaviors and neuroinflammatory processes**

Katia Befort, PhD, University of Strasbourg, France

Binge eating disorder (BED) is characterized by excessive consumption of food, usually high in sugar and/or fat, within a short period of time. BED is comorbid with other mental health conditions, including anxiety and depression, suggesting that affective processing is compromised in these patients. We assessed this proposal in a mouse model of binge eating in which animals had continuous or intermittent (4h/d) access to sucrose (17%) in a two-bottle choice paradigm. Sucrose bingeing animals displayed deficits in reward processing, an effect that was more pronounced in females. We also identified several changes in neuroinflammatory markers in reward-related brain structures, pointing to biological adaptations mediating the behavioural effects. Our work helps to characterize the impact of high-caloric intake on mental health disorders and may lead to more effective treatments for BED.

**Examining Stress-Induced Changes in 'Wanting' and 'Liking' of Palatable Food in Women with Binge Eating**
Sarah E. Racine, PhD, McGill University

This study examined whether, consistent with the incentive-sensitization theory of addiction, stress enhances 'wanting' but not 'liking' of palatable food. Participants were 153 women who spanned the spectrum of binge eating severity (i.e., from no binge eating to clinical eating disorders). Reward processing was measured across units of analysis (i.e., physiology, behavior, self-report) in the context of two experimental paradigms completed under both stressful and relaxed mood conditions. Indices of 'wanting' but not 'liking' were associated with binge eating frequency and severity, but these associations did not differ based on mood condition.

**Examining Neural Responses to Anticipating or Receiving Monetary Rewards and the Development of Binge Eating in Youth**
Lindsay Bodell, PhD, University of Western Ontario

Binge eating is characterized as eating a large amount of food and feeling a loss of control while eating. Recent neuroimaging work has suggested that increased responsivity within reward regions of the brain (e.g., ventral striatum (VS), ventral medial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), caudate) to the anticipation or receipt of rewards are related to binge eating; however, limited longitudinal data has precluded understanding of the role of reward responsivity in the development of binge eating. This study uses the Adolescent Brain Cognitive Development® (ABCD) longitudinal dataset to: (1) assess whether adolescents with binge eating have heightened neural responsivity to the anticipation (VS, caudate) or receipt (VS, caudate, vmPFC, OFC) of monetary rewards compared to matched controls; (2) whether heighted neural responsivity to the anticipation (VS, caudate) and receipt (VS, caudate, vmPFC, OFC) of rewards predicts the presence of binge eating 2 years later. Analyses are pre-registered, and findings may further our understanding of the neurobiological mechanisms underlying the development of binge eating behaviours.

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## Keynote Lecture

**Psychedelic Psychiatry – Past, Present and Future**
Dr. David Nutt, Imperial College London

Psychedelic drugs such as psilocybin and ayahuasca have been used by humans to alter consciousness for millennia. In the 1960s following the discovery of LSD the serotonin system was implicated in their actions and then a decade later this was refined to the 5-HT2A receptor where they act as agonists. But until recently their mode of action in e the brain was not understood. Over the past decade a series of neuroimaging studies mostly with fMRI have revealed how the psychedelic state emerges from stimulation of 5-HT2A receptors. These findings also open a new insight into the role of 5-HT2A-regulated brain circuits in controlling normal consciousness. It has also led to the testing of psilocybin for the treatment of depression and now other disorders such as addictions and anorexia nervosa with remarkable results. My talk will cover these topics and explore their future potential in mental health disorders as well as neurological ones
Refs
Nutt D, Erritzoe D, Carhart-Harris R, 2020, Psychedelic Psychiatry's Brave New World, *CELL*, Vol: 181, Pages: 24-28, ISSN: 0092-8674

Carhart-Harris R, Giribaldi B, Watts R, et al., 2021, Trial of Psilocybin versus Escitalopram for Depression, *New England Journal of Medicine*, Vol:384, ISSN:0028-4793, Pages:1402-1411

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## Next Generation Symposium II

### Inactivation of Cnot3 Elicits Sex-Specific Alterations in Behaviours Relevant for Autism Spectrum Disorders

Fatema El-Sayegh, Molly Zhang,Fatimeh-Frouh Taghavi-Abkuh, Argel Aguilar Valles, PhD.
Department of Neuroscience, Carleton University, Ottawa, Ontario, Canada

Introduction: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social interaction and communication and restricted and repetitive behaviors. There have been significant advances in understanding the disorder's genetic basis, and several identified genes are regulators of protein synthesis. Indeed, several de novo loss-of-function mutations in CNOT3 have been linked to ASD. CNOT3 is a non-catalytic subunit of the CCR4-NOT complex, a deadenylase that destabilizes mRNAs by shortening their poly(A) tail. However, the exact mechanism by which CNOT3 contributes to ASD remains unknown. The aim of this study is to investigate the impact of Cnot3 haploinsufficiency on ASD-related behavioral phenotypes.
Methods: To investigate the role of CNOT3 on brain development, we generated a forebrain excitatory neuron-specific mutant mouse strain by crossing a floxed Cnot3 with an Emx1-Cre mouse line. No homozygous mice were born; thus, we investigated the effect of Cnot3 haploinsufficiency on ASD-relevant behavioral phenotypes. Adult mice (aged 60-80 days) were used for behavioural tests: open field, marble burying, 3-chamber social test, self-grooming.
Results: Cnot3 haploinsufficient female mice, but not male mice, exhibited an increase in time spent self-grooming compared to control mice ($p = 0.1347$). Furthermore, Cnot3 haploinsufficient male mice displayed deficits in social novelty in the three-chamber social interaction test ($p = 0.3539$). Conclusion: Cnot3 haploinsufficiency causes deficits in social novelty but not in sociability in male mice. Moreover, Cnot3 haploinsufficiency in female mice contributes to trends in lower marble burying time and increased self-grooming behaviour. These findings shed light on effects of Cnot3 haploinsufficiency on ASD-related phenotypes.

### Correlates of Cannabis Use Disorder and Cannabis Use among Adolescents with Bipolar Disorder and Major Depressive Disorder in the National Comorbidity Survey-Adolescent Supplement (NCS-A)

Alysha A. Sultan, PhD, Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, ON, Canada; Benjamin I. Goldstein, MD PhD, [1]Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, ON, Canada, Department of Pharmacology, University of Toronto, Toronto, ON, Canada, Department of Psychiatry, University of Toronto, Toronto, ON, Canada; Carlos Blanco, PhD, National Institute on Drug Abuse and the Genetic Epidemiology Research Branch, National Institute of Mental Health, Bethesda, MD; Jian-Ping He, PhD, Genetic Epidemiology Research Branch and the Developmental Trajectories of Mental Disorders Branch, National Institute of Mental Health; Kathleen Merikangas, PhD, Genetic Epidemiology Research Branch and the Developmental Trajectories of Mental Disorders Branch, National Institute of Mental Health

Background: Despite evidence regarding prevalence and correlates of cannabis use disorder (CUD) and cannabis use (CU) in adult bipolar disorder (BD) and major depressive disorder (MDD), little is known about this topic among adolescents.

Methods: The 2001-2004 National Comorbidity Survey—Adolescent Supplement, an in-person epidemiologic survey of mental disorders, implemented a modified version of the Composite International Diagnostic Interview. Participants included adolescents, ages 13-18 years, with BD-I or BD-II (n=295), MDD (n=1112), or controls without mood disorders (n=8716). Analyses examined prevalence and correlates of CUD and CU within the BD and MDD groups.
Results: CUD was most prevalent in BD followed by MDD then controls. CU was most prevalent in MDD followed by BD then controls. In a step-wise trend BD adolescents with CUD versus CU versus no cannabis use were more likely to be female, have longer depressive episodes, lifetime history of suicide attempts, lifetime history of alcohol use disorder (AUD), and increasing rates of seeing a professional for depression. Similarly, MDD adolescents with CUD versus CU versus no cannabis use had higher lifetime rates of lifetime suicidal ideation, lifetime conduct disorder, AUD, and seeing a professional for depression, as well as lower rates of past year stimulant use.
Conclusion: CUD and CU are both associated with multiple adverse clinical characteristics in community adolescents with BD and MDD. Evidence that risks of cannabis extends across the spectrum of use is particularly important for adolescents with BD and MDD, in whom cannabis-related consequences have the potential to be more severe.

**Eye movement measures may identify potential biomarkers for adolescent depression**

Blake K. Noyes[1], BSc, Linda Booij[2], PhD, Heidi C. Riek[1], BSc, Isabell C. Pitigoi[1], BSc, Jeff Huang[1], BSc, Don C. Brien[1], PhD, Brian C. Coe[1], PhD, Brian J. White[1], PhD, Sarosh Khalid-Khan[1], MD, & Douglas P. Munoz[1], PhD. [1]. Centre for Neuroscience Studies, Queen's University, Kingston ON, Canada. [2]. Department of Psychiatry, McGill University, Montreal, QC, Canada

Introduction: Despite numerous potential biomarkers for depression having been identified, there are yet to be any widely integrated into clinical practice (Strawbridge et al., 2017), and the invasiveness of suggested techniques such as genetic analysis will pose challenges for clinical utility and patient comfort. This problem may be addressed via video-based eye-tracking; a well-established, non-invasive technique to identify alterations in neural networks responsible for cognitive control, arousal, and attention. The goal of the present study is to use eye-tracking techniques to identify potential eye movement biomarkers for depression.
Methods: The current sample includes 26 adolescents with depression (M=15.9 years, 20 female, PHQ=14.3) recruited from a psychiatric outpatient program at Kingston Health Sciences Centre and 38 controls (M=18.5 years, 31 female, PHQ=2.3) recruited from the community in Kingston, Ontario. Control participants were screened for psychiatric diagnoses using the Mini International Neuropsychiatric Interview. All participants completed self-report questionnaires for depression (PHQ-9, BDI), anxiety (BAI, GAD-7), and other mental health symptoms, as well as the Interleaved Pro-Anti Saccade eye-tracking Task (IPAST; Munoz & Everling, 2004). In this task, participants complete 240 three second trials where they are prompted to look towards (pro-saccade) or away from a peripheral stimulus (anti-saccade). Saccade behaviour, pupil size, and blink rate during IPAST will be analyzed and compared between groups.
Results: Preliminary data suggest that adolescents with depression had differential eye movement behaviour during IPAST compared to controls. Emerging trends include slower saccadic reaction time and more direction errors when making pro- and anti-saccades, increased blink rate during important visual instructions, and blunted pupil responses throughout the task. However, data collection is still ongoing. Conclusion: This preliminary data suggest that eye-tracking may be a feasible technique to distinguish adolescents with depression from healthy adolescents and identify potential eye movement biomarkers for future diagnostic purposes.

**Translocator Protein Distribution Volume, A Positron Emission Tomography Marker of Gliosis in Anorexia Nervosa**

Mariel Lepra [1,2,3] Joeffre Braga [1,2,3], Blake Woodside [3,4] Pablo M. Rusjan, [5] Rashmi de Silva Wijeyeratne, [1,2] Emily J Y Kuik, [1,2] Thomas Chao, 6 Michael Bagby, [2,3] Stephen Kish [1,2,3,4] Stefan Kloiber, [1,2,4] Ishrat Husain, [1,2,3,4] Jeffrey Meyer, [1,2,3,4] [1] Brain Health Imaging Centre, CAMH, Toronto, ON Canada [2] Campbell Family Mental Health Research Institute, CAMH, Toronto, ON Canada [3] Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON Canada [4] Department of Psychiatry, University of Toronto, Toronto, ON Canada [5] Douglas Research Centre, Montreal and Department of Psychiatry, McGill University, Montreal, QC Canada 6 Institute of Mental Health, Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada

Background: Anorexia Nervosa (AN) has a lifetime prevalence of ~0.8% and a mortality rate ~6-fold higher than the general population. Unfortunately, there are no medications indicated for AN, and there is a lack of therapeutic targets.
Presently it is unknown whether gliosis occurs in AN, but induction of brain inflammation can lead to the symptom of anorexia in rodents and AN itself is a common illness among Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS). TSPO $V_T$ can be measured using [$^{18}$F]FEPPA positron emission tomography (PET) imaging. We hypothesized that TSPO $V_T$ will be elevated in circuitry implicated in AN, including the anterior cingulate cortex (ACC), insula, dorsal putamen, dorsal caudate, orbitofrontal cortex (OFC), ventral striatum, and thalamus.
Methods: Sixteen unmedicated, nonsmoking AN (14 F, 2 M, average age 25.06) and fourteen healthy controls (11 F, 3 M, average age 25.33) underwent [$^{18}$F]FEPPA PET scanning with concurrent arterial sampling. A two-tissue compartment model was applied to measure TSPO $V_T$.
Results: There was an interaction between group and the a priori selected regions, indicating that some regions were more different between groups than others (rmANOVA, $p = 0.013$). ANOVAs comparing individual regions between groups found greater TSPO $V_T$ in ACC (40% difference, $F_{1,26} = 12.03$, $p = 0.02$), thalamus (46% difference, $F_{1,26} = 8.86$, $p = 0.006$), dorsal putamen (31%, $F_{1,26} = 14.22$, $p=0.001$), ventral striatum (37% difference, $F_{1,26} = 6.89$, $p = 0.014$), and insula (26% difference, $F_{1,26} = 6.21$, $p = 0.019$).
Conclusions: To our knowledge, this is the first investigation of gliosis in AN. Differences in TSPO $V_T$ are most prominent in the ACC and thalamus, which is strong evidence of gliosis in these brain regions. This suggests that anti-inflammatory approaches should be considered for development as treatment in AN, and that these two regions should be investigated further for evidence of inflammation and injury in AN.

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**Career Panel**

**Oh the Places You Will Go: Faculty Development and Mentorship to Support Career Success**

Dr. Shaheen Darani, University of Toronto

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*Saturday, September 23, 2023*
*Abstracts for Oral Presentations*

**Panel 3: Neural Mechanisms of Early Life Stress as a Psychiatric Risk Factor**

**Synaptic Maturation of Prefrontal Cortex Pathways Modulating Emotional Learning and Stress Sensitivity**
Dr. Maithe Arruda-Carvalho, University of Toronto Scarborough

Early life experiences crucially define cognitive and mental health function throughout life, but the precise mechanisms underlying these impacts remain unknown. Using a combination of viral tracing, optogenetic-assisted patch clamping, and chemo and optogenetic manipulations, we mapped changes in prefrontal cortex subregion synaptic transmission and probed their functional implications across the lifespan. We found age- and sex- dependent changes in the recruitment of prelimbic and infralimbic cortex projections to amygdala to fear learning and extinction in early life. Additionally, we elucidated the maturation of the dorsal peduncular cortex, an understudied prefrontal cortex subregion implicated in stress integration. Our data establish a timeline for the postnatal maturation of prefrontal circuits with critical implications for stress sensitivity and the emergence of behaviour during early life.

**Decoding the impact of social stress in adolescence on the maturing prefrontal cortex**
Dr. Cecilia Flores, McGill University

I will present data from rodent studies assessing the impact of adolescent social stress on the developing prefrontal circuit in males and females, the short and long-term behavioral outcomes, and the mechanistic underpinnings. I will show how exposure to physical/psychosocial harm in adolescence deviates the ongoing growth of dopamine axons, altering their input to the prefrontal cortex and the development of impulse control. I will show that this process is sexually dimorphic and depends on how social stress affects sociability in adolescence.

**The Long-term Impact of Early Life Stress on Serotonin Circuits and Behaviour**
Dr. Derya Sargin, University of Calgary

Serotonin is integral to development and emotional regulation, and yet we do not fully understand how early life stress (ELS) alters serotonin connectivity and results in socioemotional dysregulation. Here, using the mouse model of chronic ELS, we assessed long-term alterations to serotonin connectivity under low- and high-threat conditions. In vivo calcium imaging of the dorsal raphe nucleus revealed that ELS disrupts the serotonin response to high-threat environments. Using FosTRAP mice, we identified ELS-induced disruptions in the functional connectivity of the raphe nucleus. Next, we performed fiber photometry to determine ELS-induced changes in serotonin release in selected circuits during behavior. Overall, our findings revealed that ELS disrupts the connectivity of the serotonin system which could have implications for the treatment of affective disorders that arise from early life adversities.

## Panel 4: Novel Therapeutics for Treatment-Resistant Depression

### Nitrous Oxide Treatment for Bipolar Depression: Cerebrovascular Mechanisms

Mikaela Dimick, PhD, Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, Ontario

Summary: Nitrous oxide has shown preliminary evidence as a rapid-acting antidepressant in adults with treatment-resistant depression. This presentation will focus on findings from a randomized controlled trial of nitrous oxide treatment for refractory bipolar depression, emphasizing cerebral blood flow as a potential treatment predictor and target.

### Ketamine and Psilocybin for Treatment-Resistant Mood Disorders

Joshua Rosenblat, MD, MSc, Department of Psychiatry, University of Toronto, Ontario

Summary: Ketamine and psilocybin have shown tremendous promise for treatment-resistant depression with numerous clinical trials completed in recent years. This presentation will review findings from clinical trials and real-world effectiveness studies evaluating these novel interventions. Original data from ketamine and psilocybin trials by our group will also be presented, including a discussion of practical consideration for conducting psychedelic trials in Canada.

### Pharmacologically enhanced transcranial magnetic stimulation for major depressive disorder: safety of extended dosing with D-Cycloserine as an adjunct to intermittent theta-burst stimulation

Alexander McGirr, MD PhD, Department of Psychiatry, University of Calgary; Hotchkiss Brain Institute, Mathison Centre for Mental Health Research and Education

Summary: The recent demonstration that the treatment effects of transcranial magnetic stimulation can be pharmacologically enhanced creates opportunity for optimizing novel intersectional approaches. New unpublished data will be presented demonstrating that combining the mechanistically informed adjunct, D-Cycloserine, with intermittent theta-burst stimulation, can safely be combined for longer treatment courses and pharmacokinetic data will be presented highlighting the importance of serum concentration for this NMDA receptor partial agonist.

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*Poster Session I – Friday, September 22, 2023*
*15:00 – 16:00 – Rooms 201 and 205*

1. **Adolescent social stress alters ongoing growth of dopamine axons to the prefrontal cortex in a sex-dependent manner**

Samuel Richer, B.Sc. Integrated Program in Neuroscience, McGill University, Montreal, Quebec, Canada, Douglas Mental Health University Institute, Montreal, Quebec, Canada. Del MacGowan, M.Sc. Integrated Program in Neuroscience, McGill University, Montreal, Quebec, Canada, Douglas Mental Health University, Montreal, Quebec, Canada. Andrea H. Pantoja Urban, PhD. Integrated Program in Neuroscience, McGill University, Montreal, Quebec, Canada, Douglas Mental Health University Institute, Montreal, Quebec, Canada. Aoran Song, McGill University, Montreal, Quebec, Canada. Sehar Gul, McGill University, Montreal, Quebec, Canada. Giovanni Hernandez, PhD. Douglas Mental Health University Institute, Montreal, Québec, Canada. Cecilia Flores, PhD. Douglas Mental Health University Institute, Montreal, Quebec, Canada, Department of Psychiatry, Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada, Douglas Mental Health University Institute, Montreal, Quebec, Canada

Prefrontal cortex (PFC) development can be severely hampered by bullying in adolescence. This experience greatly impairs the PFC's role in controlling impulse behavior and often can lead to unfavourable mental health trajectories. 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 whereas females show an opposite decrease in eYFP+ axons. Aberrant DA axon innervation to the PFC induced by social adversity in adolescence may be a mechanism mediating PFC- related long-term negative outcomes associated with psychiatric risk.

2. **Exploring sex considerations in translational ASD research**

Olivia Williams*, Madeleine Coppolino, Erin Dawdy, Joshua Manduca, Colbin Perry, Tariq Akhtar, & Melissa Perreault

Background: Autism Spectrum Disorders (ASD) exhibit sex differences in age of onset, prevalence, etiology, and presentation, yet the molecular and cellular underpinnings of these differences remain unexplored. In this study, sex differences in cortical neuronal architecture, neuronal activity, oscillatory function, and behaviour, and possible molecular and cellular mechanisms were determined, and hypothesized to have sex-specific differences. Early findings

elucidating sex-specific responses from cannabis-derived cannflavins (Cann A/CannB) in an ASD model were also assessed.
Methods: In the VPA model tracing methodologies, protein abundance assays, and neurophysiological recordings in vitro and in vivo were used. The effects of CannA or CannB on these measures in primary cortical cultures or in adolescent rats were determined.
Results: In vitro studies showed that VPA-derived cortical neurons from sexed pups were less complex and showed elevated neuronal activity with greater effect in the female-derived neurons. In vivo, behavioural testing in adolescence revealed sex-specific ASD-like characteristics in the VPA group. VPA-exposed female rats displayed greater anxiety, showed deficits in recognition memory, as well as in social index scores, whereas VPA males exhibited difficulties in location memory and lower sociality. Female VPA rats displayed alterations in cortical low frequency power, however VPA elevated high frequency power in the male rats and lowered high frequency coherence between the cingulate cortex and the hippocampus. CannA or CannB treatment normalized elevations in neuronal activity in the VP-derived cortical cultures with sex-dependent effects. Preliminary in vivo findings from adolescent male and female VPA rats exposed to acute CannB administration (0.2 mg/kg i.p.) showed improved sociality in both sexes. Conclusion: These findings identify key sex differences in behaviour, and neuronal structure and function, upon exposure to VPA with more pronounced effects in female rats. This suggests that sex differences in the VPA model may have relevance to the sex-specific symptoms observed in ASD.

3. **Chronic social defeat stress dysregulates the Slit/Robo but not the Netrin-1/DCC guidance cue system in the PFC of adult female mice: implications for depression-like states**

Ashraf Mahmud[1,2], Radu Gabriel Avramescu[2], Jose Maria Restrepo[1,2], and Cecilia Flores[2,3] [1]Integrated Program in Neuroscience, McGill University, Montréal, Québec, Canada; [2]Douglas Mental Health University Institute, Montréal, Québec, Canada; [3]Department of Psychiatry and of Neurology and Neurosurgery, McGill University, Montréal, Québec, Canada

Introduction: Elevated levels of the Netrin-1 guidance cue receptor gene deleted in colorectal cancer (DCC) in the adult prefrontal cortex (PFC) is a consistent trait of major depressive disorder (MDD) and controls susceptibility to chronic social defeat stress (CSDS) in adult male mice. In contrast, the axonal guidance gene SLIT1 is downregulated in the ventromedial PFC of female, but not male patients with MDD, and in the ventromedial PFC of female and not male mice exposed to chronic variable stress (van der Zee et al., 2022). Although depression is twice more prevalent in women than men, the molecular mechanisms underlying this disparity remain unknown. Here we investigated if the Netrin-1/DCC and Slit/Roundabout (Robo) guidance cue systems are dysregulated in the PFC of adult female mice following CSDS.
Methods: Adult C57BL/6J female mice were exposed to CSDS for 10 days. Non-stressed controls were housed with a different conspecific every day. Following CSDS, mice were assessed in the social interaction test (SIT) and 24h later, PFC tissue was collected to measure mRNA and miRNA expression.
Results: Unlike control mice, susceptible and resilient mice determined by the SIT, showed increased body weight and deficits in the nestlet shredding test, a measure of self-care-like behaviour. In the PFC, there were no differences in mRNA levels among groups for either Dcc and Netrin-1 or Unc5c, another prominent Netrin-1 receptor. The expression of miR-218 – a microRNA intronically encoded in the Slit2 and Slit3 genes and repressor of Dcc, Robo1, and Robo2, was slightly elevated in susceptible mice. However, susceptible and resilient mice show elevated Slit2 and Robo1 mRNA levels in the PFC.
Conclusions: These data indicate that contrary to males, CSDS in females alters the Slit/Robo, but

not the Netrin-1/DCC guidance cue system in the PFC, possibly via currently unidentified molecular processes involving microRNAs.

4. **Association of polygenic risk for bipolar disorder with resting-state network functional connectivity in youth**

Xinyue Jiang, BSc, Clement C. Zai, PhD, MPH, Alysha A. Sultan, PhD, Mikaela K, Dimick, PhD, Yuliya S. Nikolova, PhD, Daniel Felsky, PhD, L. Trevor Young, MD, PhD, Bradley J. MacIntosh, PhD, Benjamin I. Goldstein, MD, PhD

Introduction: Little is known regarding the polygenic underpinnings of anomalous resting-state functional connectivity (rsFC) in youth bipolar disorder (BD). The current study examined the association of polygenic risk for BD (BD-PRS) with whole-brain rsFC at the large-scale network level in youth with and without BD.
Methods: 99 youth of European ancestry (56 BD, 43 healthy controls [HC]), ages 13-20 years, completed resting-state fMRI scans. BD-PRS was calculated using summary statistics from the latest adult BD genome-wide association study. Data-driven independent component analyses of the resting-state fMRI data were implemented to examine the association of BD-PRS with rsFC in the overall sample, and separately in BD and HC.
Results: In the overall sample, higher BD-PRS was associated with lower rsFC of the salience network and higher rsFC of the frontoparietal network with frontal and parietal regions. Within the BD group, higher BD-PRS was associated with higher rsFC of the default mode network with orbitofrontal cortex, and altered rsFC of the visual network with frontal and occipital regions. Within the HC group, higher BD-PRS was associated with altered rsFC of the frontoparietal network with frontal, temporal and occipital regions.
Conclusions: In conclusion, the current study found that BD-PRS calculated based on adult genetic data, was associated with altered rsFC patterns of brain networks in youth. Our findings support the usefulness of BD-PRS to investigate genetically influenced neuroimaging markers of vulnerability to BD, which can be observed in youth with BD early in their course of illness as well as in healthy youth.

5. **The association of polygenic risk for coronary artery disease with grey matter structure in youth with bipolar disorder**

Nidhi P. Kulkarni, MSc (a,b); Clement C. Zai, PhD, MPH (c,d); Kody G. Kennedy, PhD (a); L. Trevor Young, MD, PhD (b,c,d); Bradley J. MacIntosh, PhD (e,f,g); Benjamin I. Goldstein, MD, PhD (a,b,d). Affiliations: a. Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, Canada b. Department of Pharmacology & Toxicology, University of Toronto, Toronto, Canada c. Centre for Addiction and Mental Health, Toronto, ON, Canada d. Department of Psychiatry, University of Toronto, Toronto, Canada e. Sandra E Black Centre for Brain Resilience and Recovery, Sunnybrook Research Institute, Toronto, ON, Canada f. Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada g. Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Toronto, ON, Canada

Introduction: Bipolar disorder (BD) is strongly associated with heart disease and is also characterized by anomalous neurostructural phenotypes. Here we examined polygenic risk for coronary artery disease (CAD) in relation to grey matter structure in relation to youth BD.
Methods: Youth participants (mean age 17.1 years; n=66 BD, n=45 healthy controls [HC]) underwent T1-weighted magnetic resonance imaging. Polygenic risk scores for CAD (CAD-PRS) were calculated using PRS-CS-auto, based on independent adult genome-wide summary statistics. Covariate adjusted voxel-wise analyses examined the associations of CAD-PRS with cortical volume, thickness, and surface area [SA]) in the overall sample, and within BD and HC

groups. Additional regions of interest (ROI) analyses examined anterior cingulate cortex (ACC) and hippocampus. Exploratory sex-stratified analyses were also undertaken.
Results: In the overall sample, higher CAD-PRS was associated with lower right inferior temporal gyrus volume (ß=-0.32, p=0.03). Similar negative associations between CAD-PRS and brain structure were observed within the BD (5 clusters) and HC (1 cluster) groups. ROI analyses revealed a nominal association of higher CAD-PRS with lower ACC thickness in the overall sample (ß=-0.31, p[uncorrected]=0.05). Within the BD group, sex-stratified analyses revealed significant findings for females, but not for males. Conclusion: As hypothesized, higher CAD-PRS was associated with lower regional grey matter structure in youth in regions implicated in BD. Findings were more pronounced in the BD group, particularly among females. Future longitudinal studies are needed to examine the association of CAD-PRS with neurodevelopmental changes over time, and to discern mechanisms underlying the observed sex-specific findings.

6. **White matter microstructure in obesity and bipolar disorders: ENIGMA study in 2186 Individuals**

Lorielle M. F. Dietze, MSc[1,2]; Sean R. McWhinney, PhD[2]; Pauline Favre, PhD[3]; Alex Ross, BSc[2]; Ole Andreassen, MD, PhD[4]; Christopher R. K. Ching, PhD[5]; Paul M. Thompson, PhD[5]; Josselin Houenou, MD, PhD[3]; Tomas Hajek, MD, PhD[2],6; for the ENIGMA Bipolar Disorder and BMIx Working Groups7,8 [1]. Department of Medical Neuroscience, Dalhousie University, Halifax, NS, Canada. [2]. Department of Psychiatry, Dalhousie University, Halifax, NS, Canada. [3]. NeuroSpin, CEA, Université Paris-Saclay, Gif-Sur-Yvette, France. [4]. Department of Mental Health and Addiction, University of Oslo, Oslo, Norway. [5]. Imaging Genetics Center, Mark and Mary Stevens NeuroImaging and Informatics Institute, Keck School of Medicine, University of Southern California, Marina del Rey, CA, USA. 6. National Institute of Mental Health, Klecany, Czech Republic. 7. https://enigma.ini.usc.edu/ongoing/enigma-bipolar-working-group/ 8. https://enigma.ini.usc.edu/ongoing/enigma-bmix/

Introduction: Obesity affects physical, mental, and brain health. Although specific risk factors for brain changes in bipolar disorders (BD) are currently unknown, obesity is highly prevalent and could be one such factor. As medications for BD are known to contribute to weight gain, it is important to investigate the individual and combined effects of obesity, BD, and medications on white matter.
Methods: We obtained body mass index (BMI) and diffusion tensor imaging derived fractional anisotropy (FA) values from 899 individuals with BD, and 1287 control individuals from 20 cohorts in the ENIGMA-BD working group. In a mega-analysis, we investigated the impact of BMI together with other clinical and demographic characteristics on FA from 23 regions of interest (ROIs).
Results: We found that lower FA was associated with both BD and BMI in six white matter tracts, including corpus callosum and thalamic radiation. Six ROIs were correlated with only BD, white higher BMI was uniquely correlated with lower FA in three white matter ROIs. People not on lithium had a greater negative association between FA and BMI than people on lithium in the posterior thalamic radiation and sagittal stratum. In three ROIs BMI significantly mediated the negative association between medication exposure and FA.
Conclusions: For the first time we showed that both obesity and BD demonstrated lower FA in some of the same regions. The impact of obesity adds to brain changes in BD in some tracts. We observed complex patterns of associations between medications, obesity, and FA changes. Lithium treatment in some tracts protected against the negative effects of BMI. In contrast, antipsychotic and anticonvulsant related weight gain contributed to the negative associations between medications and FA. Obesity is a potential risk factor for brain changes in BD and could contribute to the negative impact of medications on the brain.

7. **Repeated exposure to delta-9 tetrahydrocannabinol in adolescence disrupts the signaling pathway that orchestrates dopamine development in a sex-specific manner**

*Tanya Capolicchio [1,2], G. HERNANDEZ[2], K. ESTRADA[2], E. DUBE[2], C. FLORES[2,3]; [1]Integrated Program in Neuroscience, McGill University, Montreal, Quebec, Canada, [2]Douglas Mental Health University Institute, Montreal, Quebec, Canada,[3]Department of Psychiatry and Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada

Introduction: Exposure to delta 9 - tetrahydrocannabinol (THC) – the main psychoactive constituent of cannabis – is steadily increasing among youth. This raises concerns because core neurodevelopmental processes occur during adolescence. Dopamine axons continue to grow from the striatum towards the prefrontal cortex across adolescence, promoting the refinement of inhibitory control. This growth is controlled by the Netrin-1 guidance receptor, deleted in colorectal cancer (DCC), whose expression in dopamine neurons is regulated by the microRNA, miR-218. Our unpublished results show that repeated exposure to THC (5 mg/kg) during adolescence alters male and female DCC receptor levels in an opposite manner, via divergent epigenetic processes. Here we investigated if these sex-specific molecular changes associate with differential THC effects on PFC dopamine and cognitive maturation.
Methods: We treated adolescent male and female C57/Bl6 mice (postnatal day 22) with 5 intraperitoneal injections of vehicle or THC (5 mg/kg) once every other day. In adulthood separate cohorts were assessed in the Go/No-go task to measure impulse control or their brains were processed to quantify the extent and organization of dopamine connectivity within the PFC.
Results: Males but not females exposed to THC show increased premature responding in the Go/No- Go task, reflective of impaired waiting impulsivity, but have fewer commission errors, indicating improved action inhibition, compared to vehicle groups. THC-treated males show a robust reduction in both the extent of the dopamine input and in the number of dopamine axon presynaptic sites in the PFC in adulthood. Conclusion: These observed changes suggest a disruption to adolescent male dopamine axon pathfinding whereas females are seemingly protected. THC in early adolescence may impact male and female dopamine and cognitive development differently and by recruiting divergent processes. DCC-mediated events may mediate outcomes in males, but in females' compensatory mechanisms may be recruited.

8. **Pilot study of circulating cell-free mtDNA in relation to brain structure in youth bipolar disorder**

Suyi Shao[1,2], BSc; Yi Zou[1], PhD; Kody G. Kennedy[1], PhD; Mikaela K. Dimick[1], PhD; Ana C. Andreazza[1,2,3], PhD; Bradley J. MacIntosh[4,5],6, PhD; Benjamin I. Goldstein[1,2,3], MD, PhD, FRCPC [1]Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, ON, Canada. [2]Department of Pharmacology & Toxicology, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada. [3]Department of Psychiatry, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, M[5]T [1]R8, Canada. [4]Heart and Stroke Foundation, Canadian Partnership for Stroke Recovery, Sunnybrook Research Institute, Toronto, ON, Canada. [5]Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada. 6Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Toronto, ON, Canada

Background: Mitochondrial dysfunction is implicated in the neuropathology of bipolar disorder (BD). Circulating cell-free mitochondrial DNA (ccf-mtDNA), reflecting mitochondrial health, has been associated with psychiatric symptoms. Current study examines ccf-mtDNA in relation to brain structure in BD.
Methods: Participants included 40 youth (BD, n=19; Control group [CG], n=21; aged 13-20). Blood samples were assayed for levels of ccf-mtDNA. T1-weighted brain images were acquired with a

3T-MRI scanner. Region of interest (ROI) analyses examined prefrontal cortex (PFC) and whole-brain gray matter cortical surface area (SA), along with vertex wise analyses. Analyses examined ccf-mtDNA main-effects and diagnosis-by-ccf-mtDNA interaction effects controlling for age, sex, and intracranial volume.
Results: In ROI analyses, higher ccf-mtDNA was associated with higher PFC SA (ß=0.33 $p<0.001$) and PFC volume (ß=0.33 $p<0.001$) within whole sample. Stratified analyses found that higher ccf-mtDNA was associated with higher PFC SA within both the BD (ß=0.41 $p=0.01$) and CG (ß=0.28 $p<0.001$). In vertex-wise analyses, higher ccf-mtDNA was associated with higher SA and volume in frontal clusters within the whole sample and within the BD group. Significant ccf-mtDNA-by-diagnosis interactions were present within 3 frontal and parietal clusters (2 for volume, 1 for SA), whereby higher ccf-mtDNA was associated with higher neurostructural metrics in the BD group but lower neurostructural metrics in CG.
Conclusions: This study found that higher ccf-mtDNA is associated with higher neurostructural metrics within the PFC among youth, with between-group divergence noted in frontal and parietal regions. Present findings, while preliminary, suggest the need for larger studies.

**9. Characterizing withdrawal from vaporized cannabis flower in adult rats**

Abdalla Albeely, Sara Hussein, Jude Frie, Hakan Kayir and Jibran Khokhar

Introduction: Cannabis use has been associated with physical dependence and withdrawal in humans. Previous studies have tried to model withdrawal in animals using repeated injections of pure synthetic ?9 tetrahydrocannabinol (THC), while little work has focused on the withdrawal effect of inhaled cannabis flowers. Considering the vast pharmacokinetic difference between the injection of THC and the inhalation of cannabis flower smoke or vapour, this study aimed to assess whether CB1 antagonist SR141716 (rimonabant) can induce precipitated withdrawal in vaporized cannabis flower exposed rats.
Methods: In this study, two groups of rats were used (a control group n=8 and a high THC cannabis group n=8) Animals received either high-THC cannabis vapour (Truro Wedding mint, 33.0% THC) (1.5 g) or air three times a day every 8 hours for 7 days. On the last day, rimonabant was administered intraperitoneally (3mg/kg) and 30 minutes later animals were recorded for 10 minutes to assess somatic signs of withdrawal (eye blinks, paw tremors, body shakes, ptosis, grooming, and scratches). The study also assessed body temperature, locomotor activity, tail flick latency as well as sucrose intake.
Results: Findings showed rimonabant induced an increase in the total number of somatic signs (eye blinking, head and body shake as well as tremors) in rats that were repeatedly exposed to high-THC cannabis vapour compared to the control rats. Further, cannabis vapour-exposed rats also showed lower sucrose intake compared to their baseline consumption showing potential anhedonia-like effects. Conclusion: Taken together, this study showed that rats repeatedly exposed to vaporized high-THC cannabis flower exhibit precipitated withdrawal.

**10. The role of serotonin axonal plasticity in fluoxetine-induced recovery in a pre-clinical model of post-stroke depression**

Sara Asgharzadeh, Mireille Daigle, Paul R. Albert. OHRI (Neuroscience), University of Ottawa Brain and Mind Research Institute, Ottawa ON, Canada

Introduction: Post-Stroke Depression (PSD) often occurs within weeks after a stroke and is associated with anxiety, cognitive impairment, poor motor recovery and increased mortality. Fluoxetine (FLX), a selective serotonin reuptake inhibitor (SSRI), is the First-line treatment for PSD, but is ineffective in half of patients. To address how FLX induces recovery, we generated a PSD mouse model by injecting endothelin-1 (ET1) into the left medial prefrontal cortex (LmPFC).

Chronic FLX treatment reversed behavioral and cognitive outcomes and this was associated with restored 5-HT projections to mPFC and other brain areas. However, the importance and mechanism through which SSRIs regenerate 5-HT projections remains unclear. Pcdha, a type of Clustered protocadherin, plays a crucial role in the development of 5-HT axons. Thus, we hypothesized that Pcdha is necessary for FLX-induced regrowth of 5-HT axons and subsequent behavioral recovery after stroke.
Methods: To examine the role of Pcdha in FLX action, we selectively knocked out the Pcdha gene in adult 5-HT neurons using TPH2-ACON mice followed by the ET1-induced stroke in the LmPFC. One-week post-stroke mice received FLX or vehicle through drinking water for 5 weeks. Anxiety and depression-related phenotypes were assessed through behavioral tests over the last 2 weeks. After the final test, brains were collected for immunofluorescence analysis, including FosB and SERT staining, to examine brain-wide activity and changes in 5-HT projections.
Results: Our results demonstrate that while FLX alleviated anxiety and depression phenotypes in wild-type mice, knockout FLX had no effect or even a detrimental effect compared to vehicle. Knockout mice showed substantial loss of Pcdhac2 in serotonin neurons, and post-stroke FLX treatment increased Pcdhac2 levels in wild-type mice but not in knockout mice. Conclusion: These findings suggest that the presence of Pcdhac2 is essential for FLX to mediate its effects on 5-HT axon regrowth and behavioral recovery after stroke.

**11. Pharmacotherapeutic effects of cannabidiol in autism spectrum disorders**
Michael Parkhill, Adina Matende, Brandon Rodrigue, Dr. Vern Lewis, Dr. Argel Aguilar-Valles

Introduction: Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterized by social deficits and restrictive/repetitive behaviour. ASD is diagnosed in roughly 1-2% of the global population. The endocannabinoid system (ECS) has recently gained interest as a potential target for treating ASD. Cannabidiol (CBD), a compound found in the Cannabis (C. Sativa) plant, is non-psychoactive and it has shown promise in ameliorating ASD-associated symptoms in Fragile X syndrome (FXS) patients.
Methods: Here, we aimed to evaluate the efficacy of CBD in treating ASD-like behaviours in Fmr1 and Shank3 knockout mice, two monogenetic animal models of ASD. To establish baseline behaviours, male and female mice from each genotype were tested in the social novelty/social preference or open field/self-grooming tests. Then, they received five daily subcutaneous injections of either vehicle or CBD (5mg/kg for males, 50mg/kg for females). An hour after the last injection, mice were tested again, as described above.
Results: At baseline, knockout mice displayed deficits in social novelty (but not social preference). Social novelty increased significantly in both KO groups following administration of CBD. Among Fmr1 KO males, scores among CBD treated mice (0.71 +/-0.04) were greater than vehicle treated mice (0.39+/-0.04) post-treatment.Similarly, among Shank3 KO mice, CBD treated mice (0.72+/-0.06) had greater SN scores than vehicle treated Shank3 mice (0.43+/-0.07). Both CBD treated KO groups had comparable scores to WT mice at baseline (0.75+/-0.03). The same trend was found among females wherein Fmr1 KO mice given CBD (0.70 +/-0.04) had greater SN scores than their vehicle treated counterparts (0.55+/-0.05). Shank3 KO females mice given CBD (0.80+/-0.06) and vehicle (0.40+/-0.05) also differed. Once again, CBD-treated KO mice had scores comparable to WT mice at baseline (0.69+/-0.06). CBD did not affect social preference, grooming, or locomotion. Conclusion: These findings suggest CBD exerts specific therapeutic effects related to social behaviour.

**12. Potential role of brain CYP2D metabolism in the development of analgesic tolerance and behavioural sensitization to orally administered oxycodone**

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Introduction: Repeated use of prescription opioids, such as oxycodone, is associated with analgesic tolerance, dose escalation and misuse; differences in their development may alter the risk of overdose. As CYP2D enzymes metabolise oral opioids and are functional in vivo in the rat brain, thereby altering local drug concentrations and responses, we hypothesized that inhibition of CYP2D in the brain would increase analgesic tolerance and locomotor sensitization following repeated oral oxycodone. Methods: Oral oxycodone (12.5-20 mg/kg gavage) was administered to male Wistar rats for 5 consecutive days and then again on challenge days 11 and 15. Analgesia was assessed using a tail-flick meter before, and 20 and 30 min after oral oxycodone to capture peak analgesia. Locomotor activity was recorded from 40-120 min. Next, propranolol (a CYP2D mechanism-based inhibitor) or vehicle pretreatment was administered intracerebroventricularly 20 hours prior to each 12.5 mg/kg oral oxycodone and assessment of behaviours. Results: In our initial dose-ranging studies, animals showed analgesic tolerance, a 75% reduction in peak analgesic response or = 20% MPE, within 5 days of exposure to 12.5-20 mg/kg of oral oxycodone; locomotor activity also increased over days 1 to 5, persisting on drug challenge days 11 and 15. In our first experimental cohort, propranolol, compared to vehicle, pretreatment showed higher initial analgesia following 12.5 mg/kg oral oxycodone and a steeper slope of analgesic tolerance; locomotor activity was higher on days 1-5 and on challenge days. Conclusion: Lower brain CYP2D activity, which can increase oxycodone in brain but not plasma, may increase initial analgesia as well as analgesic tolerance, and may increase sensitization of locomotor activity (induction and expression). Hence, those with lower brain CYP2D activity may be at greater risk of dose escalation and misuse of oral oxycodone due to a greater drop in analgesic potency and increased salience to rewarding effects.

**13. Peripheral insulin sensitivity modulates effort-based behavioural response to intranasal insulin in individuals with mood disorders**

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Introduction: Mood disorders (i.e., major depressive disorder (MDD) and bipolar disorder (BD)) and metabolic disorders (e.g., type-2 diabetes (T2D)) have a bidirectional epidemiological association. Anhedonia (i.e., the inability to feel pleasure), a core symptom of mood disorders and one often seen in T2D, results from abnormalities in the brain's rewards systems which are modulated by dopaminergic and insulin signaling pathways. To uncover neurobiological mechanisms underlying the mood-metabolic disorders comorbidity, this study investigated the role of peripheral insulin resistance (IR) in effort-based reward behaviour in individuals with mood disorders.
Methods: This randomized crossover trial assessed effort-based decision-making in seventeen participants (10 BD, 7 MDD) using the Effort-Expenditure for Rewards Task (EEfRT) in a functional MRI paradigm after intranasal insulin and placebo. Peripheral IR was calculated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR).
Results: Peripheral IR moderated the behavioural response to intranasal insulin (Condition [insulin

vs placebo] by IR interaction: Wald ?2=10.907, p<0.001). Insulin resistant participants (HOMA-IR>1.3) showed no differences in likelihood of choosing the hard over the easy task on the EEfRT between the conditions (insulin 38%, SE=6.8, placebo 41%, SE=6.6). In contrast, insulin sensitive participants (HOMA-IR<1.3) were more likely to select the hard task in the placebo (67%, SE=7.3) vs. the insulin condition (49%, SE=7.2). There were no effects of BMI and adjustments for age, sex, MADRS scores and medications did not modify the moderating effect.
Conclusions: Insulin-induced differences in reward-seeking behaviour between insulin sensitive and resistant individuals provides support for a neurobiological association between mood and metabolic disorders. The data collected from fMRI is expected to elucidate potential underlying differences in brain activity.

14. **Response to desipramine but not optogenetic stimulation in SSRI-resistant Cf1ko mice**

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Background: Major depressive disorder contributes to global disability. Selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment but have only a 30% remission rate. We have developed SSRI-resistant cF1ko mice by knockout out Freud-1, a key repressor of the 5-HT1A receptor gene, only in serotonin neurons in adulthood. This results in a less active 5-HT system associated with higher 5HT1A autoreceptors and a lower 5-HT amount in the dorsal raphe (DR). cF1ko also present altered 5-HT axonal projections resulting in a robust anxiety and depression phenotype that is resistant to chronic SSRI-fluoxetine treatment. Therefore, we used strategies to boost up or bypass the 5-HT system to promote recovery from treatment-resistant depression (TRD) in cF1ko mice. We addressed: 1-Effectiveness of chronic optogenetic stimulation of 5-HT cells located in dorsal raphe midbrain using cF1-ChR2 in which serotonin neurons were activated by light before and during behavioral testing. 2-Effectiveness of targeting other neuronal systems like the adrenergic system using chronic antidepressant desipramine treatment before and during behavioral testing.
Results: The results show that chronic opto-stimulation of 5-HT neurons did not improve the anxiety and depression phenotype in cF1ko mice. In contrast, chronic desipramine treatment reversed the cF1ko phenotype and restored deficiencies in NE axonal connectivity to inhibitory neurons in regions like mPFC, amygdala, and hippocampus suggesting that desipramine-induced NE neuroplasticity may mediate recovery in cF1ko mice. These results indicate that rather than targeting the 5-HT system in SSRI-resistant patients, antidepressants that target other monoamine systems like NE may be more effective.

15. **Antidepressant actions of optogenetic stimulation of serotonin projections to the medial prefrontal cortex in chronically stressed mice**

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Introduction: Major depressive disorder (MDD) is twice as much prevalent in females. Selective Serotonin Reuptake Inhibitors are the first-line treatment; however, only 50% of patients benefit within a 6-8-week latency. Understanding the role of specific serotonin projections in MDD could allow for better treatment options. To investigate this, we used the Unpredictable Chronic Mild Stress (UCMS) model of depression and optogenetically targeted 5-HT projections at the medial prefrontal cortex (mPFC) to promote depression recovery with reduced delay, in an all-female

cohort.
Methods: Using transgenic Cre-mediated expression of light-sensitive channelrhodopsin-2 (ChR2) in 5-HT neurons, mice were bilaterally opto-implanted in the cingulate gyrus (CG) to stimulate 5-HT projections to the mPFC during behavioural testing.
Results: Results show that the UCMS protocol induced anxiety/depression-like phenotypes as seen in coat state worsening and increased immobility duration in Tail Suspension Test (TST) (P value = 0.0001). Additionally, UCMS reduced the number of TPH+ and FosB+ cells in the dorsal raphe (DR). However, opto-stimulation at mPFC/5-HT neurons reversed behavioral effects reducing immobility duration in TST (P value = 0.0001) and increasing FosB+TPH+ cells in DR, both Dorsal (28.15 ± 10.10. P-value = 0.0317) and Ventral (17.85 ± 6.762. P-value = 0.0385) DR indicating chronic activation of 5-HT neurons in mice expressing ChR2 in serotonergic neurons.
Conclusions: Preliminary results show that UCMS induced depression/anxiety-like phenotypes. Immunohistochemistry showed that bilateral opto-stimulation of 5-HT projections to the mPFC can have downstream effects on 5-HT neurons at DR, suggesting that direct stimulation of 5-HT targeted areas like the mPFC can bypass the delayed effects of SSRIs. The future study of 5-HT axonal changes will examine wiring changes due to stress and optogenetic stimulation.

**16. Contingent versus non-contingent footshock differentially affects oral morphine consumption in a sex-dependent manner**

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Introduction: The prevalence of opioid use disorder is worsening worldwide and preclinical research on relevant sex differences in its misuse is still lacking. Prior literature also primarily utilizes intravenous self-administration (SA) despite many opioids being initially prescribed orally in the human population. Moreover, altering opioid circuitry through uncontrollable stress could expose an overlap in analgesic and reinforcement systems. The purpose of this study is to validate oral morphine (OM) SA in a time-limited operant model, like that used for intravenous research, and to assess the effects of contingent and non-contingent foot shock (FS) stress on OM SA.
Methods: Male and female rats were randomly assigned to one of five groups: Morphine Control (MC); Punishment (P); Yoked (Y); Shock Control (SC); and Chamber Control (CC). Following oral morphine acquisition, groups transitioned to the punishment phase. MC rats continued SA with no foot shocks (FS). P rats received FS at a 15% probability, contingent on active lever pressing for morphine. Y rats were matched with P to receive time-matched non-contingent FS during SA sessions. SC rats received matched FS, but never had access to morphine; CC rats never experienced FS or had access to morphine. Preliminary results: Male and female morphine controls are consuming similar amounts of drug in mg/kg. Contingent FS reduces drug intake in both, but the effect appears stronger in females. Non-contingent FS decreases consumption in males below baseline morphine control and this decrease is not observed in females.
Conclusions: The findings of this study will have important implications for the potential differential effects of punishment contingencies on activation of the oprm1 gene and morphine SA. Future research will compare baseline and post-training stress reactivity and pain responsivity via plasma corticosterone levels and tail-flick test, respectively, to determine shifts from the stressor and drug experience.

### 17. Mitochondrial enhancers for neuropsychiatric diseases

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One of the leading hypotheses of Bipolar Disorder (BD) pathology is failure of mitochondrial function to support adequate neurotransmission and synaptic plasticity, thus affecting mood regulation, memory, and executive function (Romero-Morales & Gama, 2022). The mitochondrial dysfunction hypothesis is supported by studies showing higher frequency of mitochondrial DNA (mtDNA) mutations; varying lactate levels; ROS production. Individuals with mitochondrial disease present psychiatric symptoms. It is critical to identify the potential role of mitochondrial dysfunction in in neurotransmission in patients with BD Cerebral organoids (COs) developed from patient-derived induced pluripotent stem cells (iPSCs) pose a hope to potentially model mitochondrial dysfunction and accelerate the development of mitochondrial therapies. The overall objective of this project is to identify novel mitochondrial enhancers that can restore brain mitochondrial health in BD. We hypothesize mitochondrial enhancers will ameliorate mitochondrial function in patients with BD or mitochondrial disease. We aim to restore mitochondrial health and cellular homeostasis to similar levels observed in healthy controls. In collaboration with the Applied Organoid Core at UofT, established CO models were generated from samples derived from iPSCs of patients with BD and patients with mitochondrial disease (MERRF) in comparison to healthy controls and treat with a matrix of mitochondrial enhancers such as but not limited to, ketones (beta-hydroxybutyrate) and complex antioxidant matrices (Euterpe oleraca, extract). Through this, we have successfully established a brain disease model, the COs, to study mitochondrial dysfunction where we developed COs from patients with BD and mitochondrial disease. We now aim to test various mitochondrial enhancers on neural progenitor cells, cortical neurons, and COs to examine cellular responsiveness, functionality, and overall health both before and after treatment. This is achieved through assays such as but not limited to, JC-1 for mitochondrial membrane potential, MitoTracker Red/Green for healthy mitochondria and mitochondrial mass respectively, as well as ATP production pathways.

### 18. Differential effects of adolescent THC and CBD exposure in learning and brain connectivity in adulthood

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Cannabis use is common among adolescents and the differential effects of varying cannabis constituents remain unknown. Since delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are reported to have different behavioral effects, it is imperative to investigate their differential consequences, particularly during adolescence. We aimed to investigate how exposure to 3 types of cannabis vapor in adolescent rats impacts brain development through behavioural tests and magnetic resonance imaging (MRI). We hypothesized that adolescent CBD and THC exposure will have different behavioural and brain structure and connectivity effects in adulthood. Sprague Dawley rats were divided into four groups and exposed to either high-CBD, high-THC, balanced CBD + THC, or air at post-natal days 28-42 using a vaporizer. On days 0 and 14 of exposure, rats underwent a cannabinoid tetrad test (locomotor activity, tail-flick latency, temperature, and catalepsy). In adulthood, rats underwent Pavlovian autoshaping, active avoidance, prepulse inhibition and diffusion and functional MRI analysis. Results indicated sex-dependent differences in the physiological effects of cannabis exposure in the cannabinoid tetrad test. Pavlovian

autoshaping showed that male rats exposed to high-THC and high-CBD had less lever-directed behaviour compared to controls and balanced groups, while all female rats showed no significant differences between the exposure groups. All three male cannabis exposed groups showed impaired avoidance learning. The female active avoidance data showed significant differences between the THC and CBD-exposed groups only. Both males and females showed no group differences in PPI. Regarding MRI data in male rats, we found a single network with altered functional connectivity amongst the four groups and two networks with altered structural connectivity amongst the four groups. Adolescent cannabis vapor exposure to both CBD and THC-containing cannabis can lead to long-lasting effects on behavioural, cognition, and brain structure and functionality in adulthood with clear sex differences that need to be further investigated.

**19. Role of dopamine D3 receptors in nucleus accumbens shell in conditioned memory modulation by avoidance cues**

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Introduction: Conditioned stimuli (CS) predictive of foot-shock enhance memory consolidation. Stimulating dopamine release in the shell subregion of the nucleus accumbens (NAcSh) has been shown to enhance responding to CSs. Dopamine D3 receptors (D3R) are highly expressed within the NAcSh and modulate a variety of conditioned responses. Therefore, this study was designed to test the hypothesis that D3Rs in the NAcSh are involved in the effects of CSs on memory consolidation. Methods: A signalled active avoidance procedure (30 trials/session; 0.8 mA) was employed in order to test whether the effect of a “weak” avoidance CS generated by a single session of avoidance training on the consolidation of object recognition (OR) memory could be augmented by D3R activation. Hence, immediately after the sample phase of OR, different groups of male Sprague-Dawley rats received injections of catecholamine reuptake inhibitor bupropion (BUP; 0, 5, 10 mg/kg), BUP (10 mg/kg) plus D3R antagonist NGB-2904 (NGB; 5 mg/kg), D3R agonist 7-OH-DPAT (DPAT; 0, 0.1, 1 mg/kg), or intracranial NAcSh infusions of DPAT (0, 10 ug), and were then exposed to the “weak” avoidance CS. Results: Post-sample exposure to the “weak” avoidance CS did not impact OR memory consolidation. However, post-sample administration of BUP just prior to “weak” avoidance CS exposure facilitated OR memory, and NGB blocked this effect. Post-sample exposure to the “weak” avoidance CS and concurrent systemic administration of DPAT enhanced the consolidation of object memory, and preliminary results indicate that NAcSh infusions also facilitated conditioned memory modulation. Importantly, administration of BUP, NGB, and DPAT by themselves had no effect on OR memory, indicating that D3R activation and the “weak” avoidance CS acted synergistically to impact memory. Conclusion: These data begin to elucidate neuropharmacological mechanisms through which conditioned stimuli influence the permanence of memories and provide a novel perspective to understanding conditioned psychopathologies.

**20. Developing an oral oxycodone induced conditioned place preference in rats**

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Introduction: Oxycodone is an opioid analgesic primarily taken orally but is also commonly abused. We hypothesized that oral oxycodone induces conditioned place preference (CPP) in rats. We aimed to establish a model with improved face validity (i.e., the oral route). Methods: Male rats were placed in CPP apparatus with 2 distinct compartments and habituated for 30 mins. The next day, rats were allowed to explore the apparatus for 60 minutes in a pretest after water gavage and were assigned to groups matched on preference for both compartments. The day after, rats received oxycodone (3mg/kg) or water and were confined to one compartment for 60 minutes. The treatment and compartment were alternated daily for three vehicle (water) and three oxycodone pairings (total 6 days). Over the next three days, rats received two 60 min drug free posttests followed by a state dependent test (oxycodone 3mg/kg). CPP was defined as increase in time in oxycodone versus vehicle paired compartment. Two separate very similar experiments are described: more underway. Results: In experiment 1, oral oxycodone trended to induce CPP in posttest 1 ($p=0.13$) and posttest 2 ($p=0.068$). In experiment 2, oxycodone induced CPP in both posttests ($p=0.018$, $p=0.002$). In general, the CPP was greater in the second half of the 60 min test. Locomotor activity was similar in the oxycodone and vehicle paired compartments during posttests in both experiments ($p=0.15$, $p=0.066$). Additionally, there was state dependent CPP induction in experiment 1 ($p=0.005$) but not in 2 ($p=0.33$). Conclusion: Oral oxycodone may be rewarding at this dose, and its onset may be delayed, possibly due to this oral route of administration. We will continue to develop this model with better face validity to better understand mechanisms underlying oxycodone induced reward and potentially develop more effective treatments for its abuse.

### 21. Investigating the effect of CYP2D6-mediated venlafaxine pharmacokinetics on treatment outcomes in late-life depression

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Introduction: This study aims to investigate whether CYP2D6 metabolizers have different venlafaxine (VEN)-related pharmacokinetic (PK) parameters and examine the impact of these parameters on treatment outcomes in late-life depression (LLD). We hypothesized that 1) CYP2D6 metabolizers would have different PK model-estimated VEN clearance and VEN-related drug exposure, and 2) VEN-related drug exposure would affect antidepressant treatment outcomes in LLD. Method: Participants with LLD (N=325) from a clinical trial received open-label VEN (maximum 300mg/day) for 12 weeks and were assessed for VEN and ODV plasma levels at weeks 4 and 12. We fit a non-linear mixed-effect PK model using NONMEM for VEN and ODV adjusted for CYP2D6 metabolizer status and age. Treatment efficacy was measured by Montgomery–Åsberg Depression Rating Scale (MADRS) and adverse effect was measured by UKU Side Effect Rating Scale.

Results: CYP2D6 metabolizers had significantly different PK model-estimated VEN clearance, VEN exposure, and active moiety (AM, VEN + ODV) exposure. None of the exposure was associated with treatment efficacy, including depressive symptom improvement and remission. The overall presence of adverse effects was associated with higher ODV exposure (p = 0.04, OR = 1.49 [1.03,2.16]) and higher AM exposure (p = 0.003, OR = 1.72 [1.21,2.46]). Specifically, higher VEN exposure and higher AM exposure both were associated with higher risk of nausea/vomiting (VEN exposure: p = 0.04, OR = 1.09 [1.00,1.17]; AM exposure: p = 0.01, OR = 1.98 [1.17,3.37]) and higher risk of orthostatic dizziness (VEN exposure: p = 0.02, OR = 1.09 [1.01,1.18]; ODV exposure: p = 0.01, OR = 2.00 [1.19,3.35]). Conclusion: Our study indicated that CYP2D6 metabolizers had a significant impact on PK model-estimated VEN-related PK parameters. Individuals with higher exposure were more likely to report adverse effect. Thus, older people with decreased CYP2D6 activity should be monitored due to an increased risk of VEN-caused adverse effects.

**22. Semaglutide for the treatment of cognitive dysfunction in major depressive disorder**

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Introduction: Major depressive disorder (MDD) is associated with cognitive impairments. Evidence suggests that glucagon-like peptide-1 (GLP-1) receptor agonists, such as semaglutide, may have cognitive-enhancing effects. This study is evaluating the effects of semaglutide on cognitive dysfunction in adults with MDD. Methods: This is a double-blind, randomized, placebo-controlled trial of 16 weeks of once-daily, oral semaglutide in adults with MDD. The sample has been enriched for cognitive dysfunction; only individuals with impaired executive function at baseline are eligible. The primary outcome measure is change in a composite score of cognitive tests, from baseline to week 16. Cognitive function is assessed at baseline and in-person visits on weeks 4, 10, and 16, with an additional post-endpoint assessment at week 20. Adverse events, depression scores, and suicidality is assessed at each in-person visit, as well as at bi-weekly virtual (via telephone) visits. Since February of 2022, 32 participants have been enrolled, of whom 7 withdrew prior to completing the primary endpoint. Results: In this blinded, preliminary analysis of the first 16 completers, we found significant reductions in total body weight (p = .044; mean = 7.53 lbs) and percent body-fat (p < .001; mean = 1.53%) and significant improvements in cognition, expressed as a summary of z-scores of the Digit Symbol Substitution Task, TMT-A, TMT-B, Rey Auditory Verbal Learning Task, and Stroop Task (p < .001; t = 7.18). Moreover, a significant correlation was identified between cognitive improvement and beta cell functioning (p = 0.046; r = 0.521). Conclusions: Participants in this trial had reductions in body weight and body-fat percentage, and improvements in overall cognition, which correlated with improved beta cell functioning. This study will provide insights into the potential role of semaglutide as a treatment for cognitive dysfunction in MDD and will inform future clinical practice.

### 23. Pharmacokinetic and pharmacodynamic (PKPD) analysis of antipsychotics in patients with delirium

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Abstract Introduction: Delirium incidence in acute care hospitals is high, especially among older vulnerable patients, ranging from 30% to 82% in Intensive Care Units (ICUs). It leads to far-reaching consequences such as permanent cognitive deficits, increased mortality, and rising healthcare costs. Despite extensive off-label antipsychotic use, effective therapeutic regimens for delirium remain lacking. Elderly patients experience significant changes in antipsychotic pharmacokinetics, complicating treatment. To address this, an experimental study investigated capillary blood concentrations of Pipamperone and Risperidone, including the active metabolite 9-OH-Risperidone, in elderly and younger patients.
Methods: A prospective observational study was conducted in four German hospitals from January 2021 to April 2022. Therapeutic drug monitoring (TDM) was performed on elderly hospitalized patients taking Pipamperone and Risperidone. The nonlinear mixed-effects modeling software NONMEM® was used to assess pharmacokinetics and the impact of patient-specific covariates. Capillary blood samples were collected using VAMSTM techniques and analyzed using HPLC-MS.
Results: 52 Pipamperone samples from 16 elderly hospitalized patients and 50 samples of risperidone (RIS) and 9-OH-risperidone (9-OH-RIS) from 17 subjects were collected. Additionally, 3365 plasma blood concentrations of RIS and 9-OH-RIS from 71 young healthy volunteers established a baseline compartment model in NONMEM®. The initial 1-Compartment (1-CMT) model for Pipamperone indicated an oral population clearance (CL/F) of 34.6 L/h/75 kg and a volume of distribution (Vd/F) of 515 L/75 kg. Body weight significantly impacted Pipamperone's oral clearance and volume of distribution. Conclusion: This study presents the first population pharmacokinetic model for Pipamperone in elderly delirium patients. Further investigation of these antipsychotics will optimize pharmacotherapy for delirium patients. In conclusion, this research enhances our understanding of interindividual variability in Pipamperone and Risperidone Pharmacokinetics, improving the safety of delirium treatment in senior patients.

### 24. Long-term temporal stability of 50-kHz call subtypes reveal inter-call subtype relationships but no relationship to sucrose preference

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Introduction: The sucrose preference test is a widely used measure of anhedonia in rat models of depression, yet depressed patients do not reliably show an analogous deficit. As an alternative affect-related measure, adult rat ultrasonic vocalizations (USVs) are attracting interest.
Methods: Twenty-four experimentally naive male Long– Evans rats were tested for 24 days, on alternating days of sucrose preference (12 d) and USV measurements (12 d). USVs were recorded in 20-minute sessions, and sucrose preference was measured using a simultaneous 2-bottle choice of tap water versus 0.3 % sucrose solution in 1-hour sessions. To test the longer-term temporal stability of USV emission, the rats then underwent a second round of USV measurements 3 months later.
Results: Temporally stable individual differences were revealed not only in measures of sucrose preference and 50-kHz call rates but also in the 50-kHz call profiles (i.e., the relative prevalence of

14 call subtypes). Several inter-call subtype associations were detected, including a strong negative relationship between the relative prevalence of flat and trill calls. The 50-kHz call rate was correlated with the relative prevalence of only one call subtype (short calls, negative correlation), but was positively correlated with absolute emission rates for almost all subtypes. Correlational analysis revealed no significant associations between sucrose preference and 50-kHz call rate or 50-kHz call subtype prevalence. Conclusion: On measures of sucrose preference and USV emission, adult rats maintain interindividual differences over weeks or months. This trait-like stability helped to reveal a lack of association between sucrose preference and USV measures. This lack of association is potentially significant, given the limited validity of the sucrose preference test. Therefore, USVs should be explored as an alternative measure to sucrose preference in animal models of depression. Funding: Natural Sciences and Engineering Research Council of Canada and Canadian Institutes of Health Research.

**25. Fecal microbiota transplantation from antipsychotic-naïve schizophrenia patients alters metabolic profiles differentially in male and female mice**

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Background: Emerging evidence suggests the role of gut microbiome (GMB) in the pathogenesis of schizophrenia (SCZ) and antipsychotic-induced metabolic perturbations. In the present study, we investigated the role of GMB in metabolic alterations associated with SCZ and olanzapine (a prototype antipsychotic) treatment using human fecal microbiota transplantation (FMT) in mice. Methods: FMT from AP-naïve SCZ patients (SCZ-FMT) and sex-BMI matched healthy controls (HC-FMT) were performed in 5-6 weeks old male and female germ-free C57BL/6 mice. At 10-12 weeks of age, mice were given an irradiated high-fat diet (HFD) with or without olanzapine for six weeks. Weekly food intake and body weight were monitored and an intraperitoneal glucose tolerance test (IPGTT) was performed in the last week. Circulating concentrations of glucose, insulin and free fatty acids (FFA) were measured. Homeostatic model assessment for insulin resistance (HOMA-IR), and quantitative insulin sensitivity check index (QUICKI) were calculated to assess insulin sensitivity.
Results: Female SCZ-FMT recipient mice showed significantly decreased area under the curve in IPGTT compared to HC-FMT recipient female mice ($p=0.0159$), irrespective of olanzapine treatment. This was associated with a significantly increased fasting insulin levels ($p=0.0003$), increased HOMA-IR ($p=0.0005$), and decreased QUICKI ($p=0.0004$) in female SCZ-FMT recipient mice, regardless of olanzapine treatment. Furthermore, SCZ-FMT recipient mice, regardless of sex or olanzapine treatment, showed significantly decreased serum FFA levels, which could be indicative of reduced lipolysis. Conclusion: These preliminary findings suggest that in an obesogenic environment (i.e., HFD), SCZ microbiota, and not olanzapine treatment, causes metabolic disturbances, but only in female mice. Thus, GMB could be a predisposing factor contributing to the intrinsic risk of developing type 2 diabetes associated with SCZ in females.

**26. Development of a rat model for oral operant self-administration of oxycodone: concentration-dependent consumption and session duration effects**

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Introduction: Abuse of oxycodone, a widely prescribed analgesic, has increased in recent years. We hypothesized that oxycodone self-administration intake would increase with oral oxycodone concentration. Oral administration of oxycodone is the most common route of use in humans, but there is minimal research on oral operant self-administration of oxycodone in laboratory animals. The objective of this study was to establish a rat model for the operant self-administration of oral oxycodone.
Methods: Male rats (n=16) were exposed to oxycodone solutions in drinking tubes in daily 1-2 h sessions. They were then trained to self-administer a saccharin solution (0.2%) in operant boxes for two-2h sessions before self-administration of increasing concentrations of oxycodone (0.1, 0.3, 0.6, and 1 mg/ml) during daily 3-hour sessions. Active lever presses led to delivery of the 100 µl fluid reinforcer into a trough on a fixed-ratio 1 schedule/ 5-second timeout period with light and tone cues. Inactive lever pressing had no consequence. After each session, solution remaining in the trough was measured, which was used to calculate actual consumption and intake.
Results: While increasing oxycodone concentration led to significantly decreased consumption ($p<0.05$), oxycodone intake still significantly increased with concentration ($p<0.0001$); the intake for 0.1, 0.3, 0.6, and 1 mg/ml were 0.3, 0.8, 1.2, 1.9 mg/kg respectively. While neither active ($p=0.77$) nor inactive ($p=0.85$) lever presses changed with oxycodone concentration, analysis across the 3 hours of the sessions revealed a significant increase in active lever pressing ($p<0.0001$) and a decrease in inactive lever pressing ($p<0.01$), suggesting a goal directed behaviour. Conclusion: The findings suggest that oral oxycodone self-administration may depend on oxycodone concentration and session duration. Oral operant oxycodone self-administration in rats as a preclinical model holds significant translational value and can serve as a platform for development of pharmacotherapy for prescription opiate dependence.

**27. Generalization of an interoceptive positive-feature morphine occasion setter across the rat estrous cycle**

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Introduction: Interoceptive drug stimuli may acquire conditioned modulatory properties of the induction of conditioned appetitive behaviours by exteroceptive reward cues. This effect may be modeled using a Pavlovian drug discrimination task in which an interoceptive drug stimulus is trained as a positive-feature (FP) occasion setter (OS) for an exteroceptive sucrose conditioned stimulus (CS). We have previously shown that females are less sensitive to generalization of a FP morphine OS than males, so we investigated the role of endogenous gonadal hormones in this difference.
Methods: The subjects were male and female rats, the latter of which were monitored throughout the experiment for estrous cyclicity using vaginal lavage and cytology. Rats received daily intermixed injections of 3.2mg/kg morphine or saline before training sessions. Training sessions consisted of presentations of a white noise CS followed by access to sucrose on morphine, but not saline, sessions. Following acquisition, rats were tested for generalization of the training morphine dose to 0, 1.0, 3.2, and 5.4mg/kg morphine. Females completed the generalization in vaginal metestrus, diestrus, proestrus, and estrus.
Results: All rats acquired the discrimination (Drug*Session: $P<.001$, BF10=9.50e9). Acquisition of the discrimination was similar in males and females (Sex*Drug*Session: $P=.887$, BF01=111.96) and did not fluctuate across the estrous cycle (Phase*Drug: $P=.587$, BF01=5.20). A gradient of generalization was measured across morphine doses (Dose: $P<.001$, BF10=8.44e19) and this

behaviour did not differ by sex (Sex*Dose: P=.905, BF01=7.32), nor did it differ across the estrous cycle (Phase*Dose: P=.426, BF01=4.08).
Conclusions: Morphine generalization is independent of fluctuations in levels of endogenous gonadal hormones in females under these experimental conditions. We did not replicate our previously reported sex difference in morphine generalization, but procedural modifications to the current experiment may underlie this inconsistency. Future study is required to clarify the factors mediating expression of sex differences in morphine generalization.

**28. Dopamine receptor agonism and antagonism both disrupt morphine Pavlovian drug discrimination in male and female rats**

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Introduction: One aspect of opioid use disorder is the elicitation of behaviours guided by drug-evoked stimuli. Interoceptive drug stimuli may modulate behavioural responsivity to exteroceptive drug cues through Pavlovian conditioning. To model this effect in rats, a drug state may be trained as a feature positive (FP) or feature negative (FN) occasion setter (OS) to disambiguate the relationship between a discrete conditioned stimulus (CS) and an unconditioned stimulus. Dopamine has been implicated in cued reward seeking, so we aimed to investigate its role in the functioning of a morphine drug state as a FP or FN OS.
Methods: Male and female rats were assigned to FP or FN training groups and received daily intermixed morphine or saline injections before training sessions. Training sessions consisted of presentations of a white noise CS followed by access to sucrose on morphine, but not saline sessions, for FP rats. FN rats learned the reverse contingency. Following acquisition, rats were tested for morphine stimulus discrimination after systemic pretreatment with the non-selective dopamine receptor antagonist flupenthixol, the non-selective dopamine receptor agonist apomorphine, or saline vehicle.
Results: Male and female FP and FN rats acquired the discrimination. Flupenthixol and apomorphine inhibited sucrose seeking on test trials in all rats, likely through distinct mechanisms.
Conclusions: Our findings lend support to a mechanism of OS involving gating of CS-induced dopamine release by FP or FN drug states.

**29. Altered effort-based decision-making: behavioural and neurobiological evidence of reduced effort expenditure and reward sensitivity in cannabis use disorder**

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Introduction: Cannabis use disorder (CUD) is characterized by alterations in motivation. With increasing legalization worldwide, understanding cannabis' effects on the brain is crucial. Despite mixed behavioural findings of cannabis on effort expenditure for rewards, neurobiological mechanisms underlying effort and reward valuation remain largely unexplored in this population. This study applied a functional magnetic resonance imaging (fMRI) version the Effort Expenditure for Rewards Task (EEfRT) to quantify motivation and highlight neural substrates in CUD.
Methods: 21 CUD and 20 control participants completed two runs of the EEfRT while undergoing fMRI. Repeated-measures ANOVAs tested for group differences in the number of accepted trials across effort levels and across reward magnitudes. fMRI contrasts tested for group differences during i) initial presentation of effort or reward information and ii) integration of reward or effort information. Pearson correlations were run between a priori ventral striatal ROIs and EEfRT performance.
Results: As effort levels increased, all participants made fewer high-effort choices; conversely, both groups made more high-reward choices as reward magnitude increased. Relative to controls, CUD participants made less high-effort and high-reward selections. CUD participants showed lower ventromedial prefrontal cortex activation during initial effort cues compared to controls. Initial reward cues elicited greater right insula but lower left middle temporal gyrus activation in the CUD group relative to controls. During effort-integration cues, CUD participants had greater right superior temporal gyrus activation; during reward-integration cues, CUD participants showed greater bilateral middle temporal gyrus activation relative to controls. Across both groups, increased bilateral ventral striatal activity during prospective effort correlated with the proportion of accepted high-reward tasks. Conclusion: Our findings show behavioural differences as well as neural alterations in a CUD population during prospective effort and reward processing. This work can clarify mechanisms in valuation signalling that may underly maladaptive cost-benefit decision-making in CUD.

**30. Enhancing contextual cue extinction by precipitated heroin withdrawal**

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Introduction: The recent discovery that opioid withdrawal, similarly to other states of arousal, can enhance the storage of recently acquired memories, has generated intriguing predictions relevant to addictive behaviours. More specifically, the hypothesized memory enhancing function of withdrawal suggests that memories of drug non-availability could be strengthened by post-training experiences of withdrawal, leading to enhanced extinction of drug-seeking behaviour. As such, the present study investigated the potential for precipitated opioid withdrawal to enhance the consolidation of extinction learning as it pertains to opioid-associated cues.
Methods: Male Sprague-Dawley rats underwent place conditioning with 1 mg/kg heroin (unbiased design, 4 pairings, 30 min each). To assess the memory-modulating effect of withdrawal on the extinction of the heroin-paired context, rats received immediate post-extinction injections of 0 or 3 mg/kg naloxone (NLX) with the intention to precipitate withdrawal during the critical period of memory consolidation that presumably follows extinction training sessions. Time spent in the heroin (and vehicle) paired compartments was assessed at baseline and after 5 post-extinction injections of NLX.
Results: It was found that, unlike animals injected with 0 NLX which still displayed a small preference for the heroin compartment after extinction, animals injected with 3 mg/kg NLX displayed a full reversal of the preference. Conclusion: These results suggest that precipitating opioid withdrawal post-training can effectively enhance the consolidation of extinction learning. If confirmed by additional studies, these results provide initial evidence for a ground-breaking

utilization of precipitated opioid withdrawal to prevent relapse. This research was funded by a Discovery Grant from NSERC.

**31. Electrophysiological correlates of suicide risk: A role for ketamine in suicide prevention?**

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Introduction: Suicide rates are increasing globally, yet risk mitigation strategies have been largely unsuccessful. Our objective was to (1) identify neural correlates associated with varying levels of suicide risk and (2) test effects of ketamine, a N-methyl-D-aspartate (NMDA) receptor antagonist, on activity within these neural networks. Methods: Seventy-five adults were assigned to one of four risk categories, ranging from those with a suicide attempt in the past two weeks (highest risk; n=15) to those without any psychiatric or suicide history (lowest risk; n=23). We used a CTF 275-channel whole-head magnetoencephalography (MEG) scanner to examine electrophysiological correlates of suicide. During scanning, participants completed a Life-Death Implicit Association Task, which is a computer task measuring associations of oneself to either life or death based on reaction times to words that represent each category. The D-score defined the difference in mean reaction times between self-death and self-life trials. MEG data were source-localized in the gamma (30-58 Hz) frequency, a proxy measure of excitation-inhibition balance. In a proof-of-concept open-label pilot study (N=5 highest risk), we examined changes in gamma power following subanesthetic-dose ketamine. Results: D-scores in the highest risk group did not differ from zero ($p=0.78$) but were significantly higher than the other risk groups ($ps<0.01$). Higher gamma power for self-death compared to self-life trials was found in the orbitofrontal cortex for the highest risk group ($p<0.01$) and the insula and posterior cingulate for the lowest risk group ($ps<0.05$). D-scores were not affected by ketamine administration ($p=0.57$); however, enhanced gamma power for self-death trials was found in the insula after ketamine administration compared to baseline ($p<0.001$). Conclusion: We report differential implicit cognitive processing of life and death depending on suicide risk, highlighting the need for objective measures of suicidal states. Preliminary data show promising effects of ketamine in modulating neural correlates of suicide-related cognition.

**32. NLRP3 inflammasome as a potential neuropsychiatric diseases therapy target**

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Neuropsychiatric diseases such as bipolar disorder (BD) and major depressive disorder (MDD) are complex conditions with unclear pathophysiology. There are studies demonstrating the relationship between psychiatric illnesses and inflammatory response, involving the NLRP3 inflammasome activation. In a previous study developed by our research group it was shown a specific experimental model of activating the NLRP3 inflammasome in peripheral blood mononuclear cells by emerging ASC specks. However, it would be of great interest of creating a new protocol of activating the NLRP3 in a more complex model. Cerebral organoids (COs) have been used as a modern way of mimicking brain cellular interactions. The aim of this study was to develop a new experimental model of activating the NLRP3 inflammasome in COs. COs were generated from H9-embryonic stem cells. Lipopolysaccharide (LPS) was used as the NLRP3 priming signal during 3h. Three different times of incubation (1, 4 and 16h) of nigericin was used, since nigericin is a NLRP3 assembly inductor. MCC950 was used as a well-known NLPR3 inhibitor. Interleukin (IL)-1ß, caspase-1, and immunofluorescence for ASC specks were carried

out. Statistical analyses were performed by One-way ANOVA followed by Tukey post-hoc. Results with $p<0.05$ were considered significant. It was possible to successfully generate COs composed by neurons and astrocytes (6 months old). It was observed that 3h of LPS followed by 4h of nigericin was the best condition to activate the NLRP3 inflammasome in COs, since high levels of IL-1ß and caspase-1 were found. Also, a significant emerging of ASC specks was observed at these treatments inside of the astrocytes. As expected MCC950 was capable of reducing IL-1ß and caspase-1, while decreasing ASC specks compared to LPS+nigericin group. The obtained results prove that it was possible to reproduce the NLRP3 inflammasome activation in COs, being this a potential target for anti-inflammatory drug screenings.

### 33. Exploring the effects of sweet additives in a novel oral morphine self-administration model

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Introduction: Morphine is an opioid analgesic most often consumed orally but rarely administered via this route in preclinical literature. To increase translatability, we previously developed a two-lever self-administration model using an oral reinforcer solution containing morphine and grapefruit juice (GFJ) in water as GFJ is thought to increase the bioavailability of morphine. A sucrose (SUC) fading procedure was employed to overcome the bitter taste of morphine. However, conclusions on the reinforcing properties of morphine based on our model are obfuscated by these sweet additives. The present study aims to determine the behavioural outcomes of manipulating each component of this reinforcer solution.
Methods: Male and female rats underwent daily self-administration sessions on a fixed ratio 1 reinforcement schedule during which they were trained to lever press for brief access to a 0.5g/L morphine solution. A 20-session SUC fading procedure (20%, 10%, 5%) was used to facilitate the acquisition of morphine self-administration; then 5 phases of consumption testing, each lasting 10 sessions, were conducted: Phase 1: water+morphine; Phase 2: 5%SUC+morphine; Phase 3: GFJ+morphine; Phase 4: 5%SUC+GFJ+morphine; and Phase 5: GFJ+water. Saphenous blood samples were taken immediately after the final sessions of phases 2-4 to assess serum levels of morphine. Preliminary
Results: Consumption (mg/kg) was stable for both sexes at 20%, 10%, and 5%SUC concentrations; however, when SUC was removed from the morphine, consumption decreased. Addition of GFJ to the morphine did not rescue this decrease, but GFJ is expected to increase consumption of 5%SUC+morphine. We also expect adding GFJ to 5%SUC+morphine will increase plasma levels of morphine.
Conclusions: Acquisition of stable oral morphine consumption in all phases does not appear to be strongly driven by sex but is likely influenced by vehicle sweetness and modulation of morphine pharmacokinetics by GFJ.

### 34. Positive- or negative-feature conditioning with morphine differentially influences morphine reward in female rats

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Background: The interoceptive cues elicited by morphine can disambiguate relationships between conditioned stimuli (CS) and unconditioned stimuli by functioning as a positive-feature (FP) or negative-feature (FN) occasion setter (OS). OS conditioning of exteroceptive stimuli results in attribution of incentive salience characteristics to those stimuli. The aim of this study was to assess the effect of morphine OS training on subsequent morphine reward.
Methods: Male and female rats were randomly assigned to FP, FN, or control groups. Daily intermixed injections of 3.2mg/kg morphine or saline were administered to FN and FP groups before each of 32 training sessions, during which a white noise CS signalled the presence or absence of a 26% sucrose solution US. On morphine, but not saline sessions, the CS was followed by access to sucrose for FP rats, whereas this contingency was reversed for FN rats. Controls received saline prior to all sessions. Training was followed by an 11-session place conditioning procedure in which 3.2mg/kg morphine was paired with one distinct side of a 2-sided chamber for 8 sessions. Preference tests, in which rats had free access to both sides of the chamber, were conducted on sessions 1, 6, and 11.
Results: FP and FN contingencies were acquired by both sexes. Males preferred the morphine-paired side of the chamber regardless of training history. Female controls preferred the morphine-paired side, and this preference was acquired more quickly in FP rats. Female FN rats did not develop a preference to the morphine-paired side. Conclusion: Training history with morphine as an occasion setter influences morphine reward in females but not males. The effects of appetitive and inhibitory morphine associations on morphine reward may be pertinent to the treatment of opioid use disorder in women.

**35. Decoding the neural representation of value in schizophrenia**

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Introduction: Deficits in pleasure and motivation are prevalent in many neuropsychiatric conditions such as schizophrenia with negative symptoms. Here we have developed a novel fMRI task combined with multivariate pattern analysis (MVPA) approaches to study the neural mechanisms of value-based decision making that may underlie negative symptoms of schizophrenia. Methods: The "Movie Shopping" fMRI task is designed to simultaneously probe the multiple aspects of value-based decision making including experience of pleasure, value representation, and motivation. During fMRI acquisition participants watch a movie trailer (experience of pleasure), report their enjoyment of the trailer and bid real money to try and win the movie advertised (following the Becker-Degroot-Marschak procedure, to determine their willingness-to-pay). Participants can also win the movie by making repeated key presses (assessing willingness-to-work). This is repeated for 90 trials. Data was available for 15 controls and 10 patients. Results: Using MVPA, patterns of brain activity were identified in two groups (healthy controls and schizophrenia patients) and related to willingness-to-pay. Preliminary results showed patterns of brain activity in the ventromedial prefrontal cortex during movie trailer viewing ($t14=3.36$, $p=0.002$) and auction period ($t14=1.92$, $p=0.03$, 1-sample t-tests) significantly predicted financial decisions in the control group. Compared to controls, patterns of brain activity were significantly less predictive of willingness-to-pay in the schizophrenia group (during trailer viewing, $t23=2.21$, $p=0.03$ and auction period, $t23=2.21$, $p=0.03$, 2-sample t-tests.) Conclusion: The preliminary results of this study show that individuals with schizophrenia have deficits in value representation

compared to healthy individuals, consistent with models of the neural mechanisms of negative symptoms.

### 36. The association between blood biomarkers and brain white matter and myelin content in bipolar disorder: a systematic review

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Introduction: Individuals with bipolar disorder (BD) often experience difficulties with cognitive functioning and emotional processing, which suggest underlying abnormalities in brain morphology and function. Studies using diffusion tensor imaging (DTI) have demonstrated abnormalities in white matter (WM) microstructure, which recently have been found to be associated with a wide array of blood-based biomarkers. The purpose of this systematic review is to investigate the potential association between blood-based biomarkers and WM in BD, which together can potentially lead to the identification of knowledge gaps in the literature and guide future studies.
Methods: This systematic review was registered on PROSPERO international prospective register of systematic reviews (ID Number: 42021279246). Three databases were used for this systematic review: PubMed, Embase, and PsychINFO. No restrictions on date of publication, language, or geographical location were used. Studies that presented original data and investigated both a blood-based biomarker and a neuroimaging technique of WM and myelin content in patients with BD were included.
Results: The literature search yielded 3270 studies, of which 918 were duplicates. Hand searches were also conducted to identify any additional studies (n=4). 2356 articles were screened, and a total of 17 studies were included in the systematic review. Several classes of biomarkers were found to be associated with WM in BD, which includes kynurenine pathway (5-hydroxy indole acetic acid, Kynurenic Acid), innate immune system (Natural Killer cells), cytokines and growth factors (Interleukin 8, Tumor Necrosis Factor Alpha, and Insulin-like growth factor binding protein 3), various gene polymorphisms (Serotonin-Transporter-Linked Promoter Region), and metabolic markers (Lipid Hydroperoxidase, Cholesterol, triglycerides). Conclusion: This systematic review found that blood-based biomarkers were shown to be associated with markers of WM deficits observed in BD. Further studies including longitudinal studies investigating the potential clinical utility of blood-based biomarkers are encouraged.

### 37. High-throughput analysis of peripheral blood microRNA profiles as biomarkers for depression risk in children and adolescents

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Background: Discovering objective molecular markers of psychiatric risk, particularly complemented with longitudinal clinical records, will aid early prevention and intervention. Emerging role of microRNAs in neurodevelopment and mental illness warrants a non-invasive investigation focused on early life. In this study we conducted a high-throughput analysis of microRNA profiles in peripheral fluids derived from blood in children and adolescents with or without clinical levels of depression.
Methods: The study utilized a small RNA protocol to sequence a total of 60 dried blood spot samples from the Teen Inflammation Glutamate Emotion Research (TIGER) cohort and 170 blood plasma samples from the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) cohort. The trimmed reads underwent processing using the exceRpt small RNA-Seq pipeline, and differential expression analysis was performed using the DESeq2 package. Categorical groups were assigned based on the clinical diagnosis and the Reynolds Adolescent Depression Scale (RADS) or the threshold-based Child Depression Inventory (CDI) measures in the TIGER and GUSTO cohorts, respectively.
Results: Multiple differentially expressed (DE) microRNAs (padj<0.05) were discovered, exhibiting upregulation in individuals diagnosed with MDD compared to controls, and predominantly downregulation in children with low CDI compared to those with high CDI. A shared microRNA (p<0.05) displayed upregulation in both cohorts. Gene ontology analysis, utilizing predicted targets of the DE microRNAs confirmed their association with MDD and also revealed implications in cardiomuscular biological processes.
Conclusions: To our knowledge, this is the first investigation of blood microRNA expression signatures of depression in youth. Identified microRNA profiles will serve as the basis of gene target prediction and creation of expression-based gene networks within brain regions relevant in depression, which will improve our understanding of the functional mechanisms underlying psychiatric vulnerability in adolescence.

### 38. Altered inhibitory control across three major neuropsychiatric disorders revealed through video-based eye tracking

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Introduction: Inhibitory control is a fundamental cognitive domain that can be assessed using simple eye tracking tasks such as the interleaved pro/anti-saccade task (IPAST; look towards versus away from a peripheral stimulus). Attention-deficit hyperactivity disorder (ADHD), bipolar disorder (BD) and borderline personality disorder (BPD) are three prevalent neuropsychiatric disorders that are each characterized by deficient inhibitory control. However, no study has directly compared IPAST performance across these three clinical groups. The aim of this study was to use the IPAST to determine the extent to which inhibitory deficits are similar or divergent across adults with ADHD, BD, and BPD.

Methods: Video-based eye tracking was used to record eye movements in 104 healthy adults, 20 adults with ADHD, 51 adults with BD, and 20 adults with BPD while they performed the IPAST. Numerous parameters of visuomotor and cognitive control were derived from the task and compared between groups. Factor analysis was performed to investigate the latent variables underlying task performance across participants, as well as their associations with clinical measures.
Results: Comparison of IPAST parameters between groups indicated that, relative to control participants, ADHD participants made more long-latency direction errors, BD participants made more direction errors overall and exhibited more impulsive pre-stimulus behaviour, and BPD participants made more short-latency direction errors. Notably, clinical groups did not differ from one another. Factor analysis and correlation of clinical measures across groups revealed latent variables underlying task performance that were associated with symptoms of inattention, impulsivity, and anxiety, as well as psychotropic medication use. Conclusion: Our findings indicate that adults with ADHD, BD, and BPD share similar inhibitory control deficits, as measured by the IPAST, suggesting common dysregulation in fronto-striatal pathways of the brain. The specific IPAST parameters altered in each clinical group point to different vulnerabilities in attentional, inhibitory, and voluntary brain processes.

### 39. Preliminary evidence of CBD expectancy effects on amygdala functional connectivity with the anterior cingulate cortex

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Introduction: Cannabidiol (CBD) has been shown to impact brain regions that are implicated in anxiety and stress-reactivity (e.g., amygdala, anterior cingulate cortex [ACC], anterior insula [AI]). Our group has previously demonstrated that CBD expectancy alone is sufficient to alter subjective, physiological, and endocrine markers of stress and anxiety; however, it is unclear to what extent these findings reflect altered brain reactivity. This study aimed to determine whether CBD expectancy independently alters amygdala resting-state functional connectivity (rsFC) with the ACC and AI following an acute psychosocial stressor. Method: 37 (20 female) healthy adults were randomly assigned to receive either accurate or inaccurate information regarding the CBD content of a CBD-free oil that was administered during a single experimental session. Following a baseline resting state MRI scan, participants administered their assigned oil sublingually. Participants then engaged in stress task (serial subtraction with negative feedback) inside the scanner, and underwent a second resting state scan. Amygdala rsFC with the ACC and AI was assessed during each MRI scan, and outcomes were assessed using ANCOVA.
Results: CBD expectancy was associated with reduced rsFC between the left amygdala and right ACC at a trend level (p=.088), while controlling for individual differences at baseline. Post-hoc within-condition pairwise comparisons demonstrate a significant reduction in rsFC of these regions in the told CBD condition (p=.009), but not the told CBD-free condition (p=.531). CBD expectancy did not systematically impact amygdala-AI rsFC. Conclusion: To our knowledge, this is the first study to explore the neural substrates of CBD-related placebo effects. While underpowered to detect subtle effects, these preliminary findings suggest that CBD expectancy may be sufficient to alter neural responses relevant to its purported anxiolytic and stress-relieving properties. Future work is needed to replicate these results and determine whether CBD expectancy and pharmacology interact to alter anxiety and stress-reactivity in the brain.

### 40. Lipid peroxidation and brain structure in youth bipolar disorder

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Introduction: Lipid peroxidation is a potential biomarker of bipolar disorder (BD) neuropathology, and has been linked with neuroimaging phenotypes. Little is known about this topic in youth. We examined lipid hydroperoxidases (LPH) and 8-isoprostane (8-ISO) in relation to brain structure in youth with BD and healthy controls (HC).
Methods: A total of 94 youth (BD = 49; HC = 45) between the ages of 13-20 years were included. Blood levels of LPH and 8-ISO were assayed. Structural measures of cortical thickness, surface area, and volume were measured via 3T MRI. Covariate-adjusted general linear models were used for regions of interest (ROI) (prefrontal cortex, hippocampus and anterior cingulate cortex (ACC)) analyses and vertex-wise analysis.
Results: ROI analysis revealed that greater LPH concentration was associated with greater ACC thickness in BD youth (B = 0.43; p = 0.01) but not HC youth (B= 0.15; p = 0.44). Vertex-wise analysis revealed identified 18 significant clusters. Higher LPH concentration was associated with greater regional cortical thickness across the overall sample, and in the BD and HC groups as well as smaller regional volumes within the overall sample and HC group, while an inverse relationship was observed for 8-ISO. Both LPH and 8-ISO concentrations were associated with smaller surface area within the overall sample and within the HC group compared to the BD group but only for LPH. Conclusion: This preliminary evidence suggests that changes in LPH and 8-ISO concentrations are related to brain structure in BD vs HC patients. Further studies incorporating neuroimaging and oxidative stress biomarkers are warranted.

### 41. Allyl isothiocyanate (TRPA1 agonist) protected against olanzapine-induced metabolic alterations in mice

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Background: Olanzapine is one of the commonly prescribed atypical antipsychotics but has a higher propensity of inducing severe metabolic adverse effects such as obesity and type 2 diabetes. Allyl isothiocyanate (AITC) is an agonist of transient receptor potential ankyrin 1 (TRPA1) channel and has been reported to have antidiabetic and antiobesity potential in rodents as well as in humans. The present study was aimed to investigate the role of TRPA1 channels in

olanzapine-induced metabolic alterations in mice. Methods: Female BALB/c mice were treated with olanzapine, AITC, and HC-030031 (TRPA1 antagonist) for 6 weeks. Locomotor activity in open field test, weekly body temperature, and feed intake were measured. Biochemical/molecular metabolic parameters were estimated in serum, liver and hypothalamus. Results: AITC co-treatment protected against chronic olanzapine-induced metabolic alterations mainly by restoring reduced locomotion and body temperature, increased serum glucose, lipids, insulin, proinflammatory cytokines, and liver glycogen levels. AITC treatment protected against olanzapine induced insulin resistance and glucose intolerance in the oral glucose tolerance test. These peripheral changes were associated with altered mRNA expression of hypothalamic appetite-regulating, nutrient-sensing and inflammatory markers, which were reversed by AITC treatment. Interestingly, olanzapine treatment reduced TRPA1 mRNA expression in the hypothalamus indicating its role in inducing metabolic alterations. Additionally, olanzapine induced mRNA expression of hepatic lipogenesis enzymes while reducing lipolytic enzymes expression consequently higher lipid accumulation in liver as evident by histological analysis. Furthermore, antidiabetic and antiobesity effects of AITC were differentially abolished in the presence of HC-030031. Conclusion: Our preliminary results suggested the protective effects of AITC against olanzapine-induced metabolic alterations, which were likely to be TRPA1 dependent. Further studies are needed to investigate the molecular interactions between TRPA1 channels and antipsychotics. Keywords- TRPA1 channels, Allyl isothiocyanate, antipsychotics, Olanzapine, metabolism, insulin resistance, type 2 diabetes

### 42. Examining the link between diet and mitochondrial biomarkers in individuals with bipolar disorder

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Introduction: Mood disorders, specifically bipolar disorder is a chronic psychiatric disease affecting approximately 1% of the global population and is traditionally defined by fluctuating episodes of mania and depression. Bipolar disorder patients have consistently displayed high rates of metabolic syndrome, impaired glucose tolerance, type 2 diabetes, and obesity. The brain is the biggest utilizer of to support adequate function, neurotransmission, cognition, and memory. This link between bipolar disorder and this altered metabolic state is mitochondrial metabolism. An efficient way to examine and alter energy metabolism is through diet. Diet has the capability to enhance mitochondrial health and function, improve inflammation, modulate the gut microbiota, and potentially act as a therapeutic to improve the course of chronic diseases like bipolar disorder. Methods: In collaboration with the FondaMental Foundation, we will be utilizing various statistical tests to assess dietary data from patients with bipolar disorder. We will be modelling these dietary results in vitro using neuroprogenitor cells (NPCs), to assess functional mitochondrial endpoints. Results: Several different dietary endpoints we assessed including the consumption of meat, simple carbohydrates, seafood, dairy, and isoflavone rich food. The consumption of isoflavone rich food, when analyzed against simple carbohydrates is tightly correlated to improved mood, reduced incidence of metabolic syndrome and a lower incidence of hospitalizations per year. Results mimicking this scenario in vitro, with patient-derived NPCs and evaluating isoflavones acting as a mitochondrial therapeutic, are pending. Conclusion: We aim to highlight the importance of diet, and diet-derived therapeutics, and its capability of improving mitochondrial health in bipolar disorder, and modifying the course of brain diseases.

### 43. Targeting ERK signalling in fragile X syndrome and autism

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Introduction: Autism is one of the most prevalent neurodevelopmental disorders both in Canada and worldwide. Fragile X Syndrome (FXS) is the most common genetic cause of autism and intellectual disability. Increased activation of extracellular signal-regulated kinase (ERK) signalling in the brain is observed in both patients and animal models of these conditions. It has been proposed to be a critical node, upon which different risk factors and associated intracellular pathways converge and lead to the phenotypic alterations. We hypothesized that selectively targeting this pathway could reverse core condition-modelling phenotypes in animal models of autism and FXS. Methods: Here we tested a clinically relevant, selective inhibitor of ERK signaling in two mouse models, one for FXS and one for idiopathic autism. Results: We report that treatment with this inhibitor robustly reduced ERK activation in the brain, and reversed core phenotypes in behavioral and electrophysiological domains in both models. Additionally, the inhibitor treatment reduced eIF4E activation, a key translation initiation factor and a downstream target of ERK, in both models. Further analysis revealed that the treatment did not cause apparent side effects, or affect the control animals. Conclusions: Our data indicated that selectively inhibiting ERK signalling was beneficial in both models. These results further support the notion that dysregulation in ERK pathway causally contributes to the pathophysiology of autism and FXS. They also suggest that selectively targeting ERK signalling could be a new approach for treating these conditions.

### 44. Amphetamine in adolescence induces a male-specific mesolimbic dopamine phenotype in the adult prefrontal cortex

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Introduction: During adolescence, the mesocorticolimbic dopamine (DA) system undergoes significant maturational changes. In male but no female mice, early adolescent exposure to recreational like doses of amphetamine (AMPH), causes ectopic growth of nucleus accumbens (NAcc) DA axons to the PFC. This effect is mediated by drug-induced downregulation of the Netrin-1/DCC guidance cue system and leads to male-specific cognitive dysfunction (Reynolds, Hernandez et al 2023, Nat Comm). We investigated whether the presence of NAcc DA axons in the PFC alter DA transporter (DAT) expression, baseline DA kinetics, and DA signaling in response to methylphenidate (MPH) and could be prevented by DCC receptor upregulating in adolescence using CRISPRa. Methods: Male and female mice were injected (i.p.) with saline (SAL) or AMPH (4 mg/kg) from PND 22 to PND 31 and placed in distinctive compartments of a place-preference box. Preference was assessed at PND 32 and PND 80. One day later, the DA sensor GrabDA2h was microinjected, and an optical fiber was implanted into the PFC. DA dynamics were measured with fiber photometry at baseline, following acute i.p. injections of SAL and MPH (10 mg/kg). In a separate cohort of male mice, CRISPRa for Dcc or LacZ control was microinjected into the ventral tegmental area at PND 21, followed by AMPH or SAL treatment. Results: Male and female mice exhibited short- and long-lasting AMPH place-preference. However, only AMPH-treated males displayed increased PFC DAT density, along with decreased

baseline DA transients, increased amplitude, faster DA release, and an exaggerated PFC DA signal response to MPH. DCC upregulation prevented place-preference development and alterations in DA dynamics. Conclusion: NAcc DA axons ectopically innervating the PFC seems to retain the properties of their intended target. This phenotype is likely to underlie male-specific vulnerability to detrimental effects of AMPH on cognitive development.

## *Poster Session 2 – Friday, September 22, 2023*
## *16:15 – 17:15 – Rooms 201 and 205*

1. **Adult rat ultrasonic vocalizations as potential markers of affect: effects of propranolol and repeated cocaine administration**

Leyla Erden, BSc, Adithi Sundarakrishnan, BSc, Paul B.S. Clarke, PhD

Introduction: Pharmacological mechanisms underlying psychostimulant euphoria remain poorly understood. In adult rats, the positive emotional states produced by certain addictive drugs are accompanied by alterations in 50-kHz ultrasonic vocalizations (USVs): specifically, the "trill" call subtype becomes more prevalent, at the expense of "flat" calls. Here, we investigated the effects of repeated cocaine administration, and – based on findings with amphetamine – their possible dependence on beta-adrenergic receptors.
Methods: Male Long-Evans rats received cocaine (10 mg/kg i.p.) or saline before daily 30-min locomotion/USV recording sessions. Phase 1 examined cocaine's initial effects and their change with chronic administration. Phase 2 tested for interactions between propranolol pretreatment and cocaine or amphetamine challenge. In Phase 3, propranolol/cocaine interactions were sought within a CPP procedure.
Results: Cocaine's locomotor stimulant effect was accentuated by propranolol. In Phases 1 and 2, cocaine increased the 50-kHz call rate, with apparent sensitization, but did not alter flat vs. trill call prevalence. In Phase 3, cocaine again increased the 50-kHz call rate, but now clearly promoted trills (associated with positive affect) and suppressed flat calls, also exerting novel effects on other USV subtypes. Propranolol exerted several significant USV-related effects when given alone, but did not prevent any of cocaine's behavioural effects, i.e. on USV emission, locomotor activity or CPP.
Conclusions: Cocaine markedly increased the 50-kHz call rate and, with repeated testing, altered the relative prevalence of several USV subtypes. Notably, cocaine promoted trill calls at the expense of flat calls – as previously seen with other positive emotional states. The beta-blocker propranolol, which was clearly behaviourally active, failed to inhibit cocaine's effects. Further, our results revealed some evidence for sensitization to cocaine's behavioural stimulant effects. Adult rat 50-kHz USVs offer a wealth of information beyond conventional behavioural tests, potentially providing a window on affective changes of possible relevance to human drug use/abuse.

2. **24-hour rhythmicity of affective, cognitive, and somatic symptoms in major depressive disorder: an interim analysis**

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Introduction: Major depressive disorder (MDD) affects over 300 million people worldwide, with circadian rhythm abnormalities potentially contributing to symptom perception. The Mood Rhythm Instrument (MRhI) was developed to evaluate 24-hour rhythmicity of mood-related symptoms, encompassing affective, cognitive, and somatic symptom domains. The current study assesses the perception of symptom rhythmicity using the MRhI in a clinical sample of Canadians with MDD.
Methods: Participants were recruited through online and community advertisements and

recruitment is ongoing. Psychiatric diagnoses were assessed using the Mini International Neuropsychiatric Interview. The MRhI was administered to evaluate perceived symptom rhythmicity over the past 15 days. Differences in frequency of peaks between three groups (healthy controls (HC), MDD (euthymic), and MDD (depressed)) were assessed using Fisher's test and timing using the Watson-Wheeler test.
Results: This interim sample includes 174 participants: 73 HC (74% female, ages 18-72, mean±SD=35±15), 40 with remitted depression (68% female, ages 17-68, mean±SD=35±15), and 61 with current depression (64% female, ages 17-70, mean±SD=38±14)). The HC group was less likely to report peaks than the euthymic and depressed MDD groups for anxiety ($p<0.001$), sadness ($p<0.001$), and energy ($p<0.01$). The HC group was also less likely to report peaks in self-esteem ($p<0.05$) and ability to solve problems ($p<0.01$) when compared to the euthymic MDD group. The depressed MDD group was more likely to report peaks in irritability than the euthymic MDD group ($p<0.01$). Timing of peaks did not differ between groups.
Conclusions: Individuals with past and current depression are more likely to perceive the 24-hour rhythmicity of several affective, cognitive, and somatic symptoms. Similar findings were observed in non-clinical samples from Spanish, Brazilian, and Canadian populations. Future analyses will explore the correlation between peak frequency/timing and depressive symptom severity.

### 3. Longitudinal inference of hippocampal volume and morphometric hippocampal-cortical connectivity in psychotic disorders

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Introduction: Hippocampal volume and hippocampal-cortical connectivity are significantly reduced in psychosis. Yet, the temporal order in which these two deteriorate across subtypes of psychosis remains to be determined. To this end, we implemented SuStaIn, a machine-learning algorithm which uniquely combines disease progression modeling and clustering. Methods: We sampled cross-sectional data from 175 patients with psychosis and 117 non-clinical controls from two datasets on first- and multi-episode psychosis. 18 hippocampal volumes were extracted through the MAGeT-algorithm and CIVET-derived cortical thickness values were parcellated into 62 DKT-regions. Structural covariances and then subject-specific structural covariance matrices were extracted for patients and controls by the means of the Jackknife Bias Estimation procedure. Hippocampal-cortical connectivity was then derived through the graph-theoretical participation coefficient after grouping the 18 hippocampal regions into a hippocampal module and estimating the inter-modular connectivity with the 7 Yeo networks. SuStaIn was implemented across three separate analyses. The first analysis combined 8 measures of (bilateral white matter and subfield) volume and connectivity, while two follow-up analyses examined the 18 volumes and 18 participation coefficients separately. Results: Following 10-fold cross-validation, SuStaIn revealed two subtypes in which either deteriorated white matter or subfield volume preceded deteriorations in hippocampal-cortical connectivity. The follow-up analyses showed that reductions in subfield volume preceded either no further deteriorations in connectivity, deteriorations of the input regions or across broad regions of the hippocampus. Reductions in white matter volume were followed by connectivity deteriorations in either the left hemisphere, in input regions or broadly across the hippocampus. Conclusions: These findings show that hippocampal volume deteriorates prior to

morphometric hippocampal-cortical connectivity. Further, a deterioration of subfield volume can but does not need to evoke deteriorations in connectivity, while a deterioration of white matter volume necessarily does. These findings provide distinguishable neural pathways which might underlie the heterogeneous clinical presentation of psychotic disorders.

4. **Suicidality is associated with heightened impulsivity and stress in individuals with GD**

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Introduction: Gambling Disorder (GD) describes repeated, harmful gambling behaviour that is associated with higher suicidality than substance use disorders or the general population. Prior GD research suggests heightened impulsivity in individuals who have attempted suicide. However, currently, no research examines how stress characteristics might differ amongst individuals at risk for suicide. This pilot GD investigation examined perceived stress over the past 30 days and the effects of acute stress in individuals endorsing (SI) or not endorsing suicidality (NS).
Methods: Individuals with GD (N=41) were divided into an SI group and an NS group. Group differences were tested for gambling severity, impulsivity, perceived stress, and gambling-related cognitions. A subset of this sample (n=19) underwent an acute stressor, after which mood disturbance measures were taken.
Results: Results show that 70.7% (n=29) of the sample endorsed suicidality in their lifetime. Gambling severity and gambling-related cognition scale scores did not differ between the SI and NS groups, though gambling severity did trend higher for the SI group. The SI group had higher impulsivity scores, driven by Nonplanning and Negative Urgency subscales, and reported greater perceived stress over the past 30 days. While the acute stressor did not produce statistically significant group differences, the SI group showed a trend of heightened mood disturbance over time with less responsiveness to the acute stressor.
Conclusions: These findings suggest that more severe gambling problems cannot sufficiently explain suicide risk amongst individuals with GD. Specific impulsivity facets, namely Nonplanning and Negative Urgency, are closely related to suicide risk, as was perceived 30-day stress. The acute stress data suggest potentially altered stress processing in the SI group. A better understanding of altered stress and stress processing will be important to understand the underlying processes contributing to suicidality amongst individuals with GD.

5. **Translocator protein distribution volume: a positron emission tomography marker of gliosis in anorexia nervosa**

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Background: Anorexia Nervosa (AN) has a lifetime prevalence of ~0.8% and a mortality rate ~6-fold higher than the general population. Unfortunately, there are no medications indicated for AN, and there is a lack of therapeutic targets.

Presently it is unknown whether gliosis occurs in AN, but induction of brain inflammation can lead to the symptom of anorexia in rodents and AN itself is a common illness among Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS). TSPO $V_T$ can be measured using [$^{18}$F]FEPPA positron emission tomography (PET) imaging. We hypothesized that TSPO $V_T$ will be elevated in circuitry implicated in AN, including the anterior cingulate cortex (ACC), insula, dorsal putamen, dorsal caudate, orbitofrontal cortex (OFC), ventral striatum, and thalamus.
Methods: Sixteen unmedicated, nonsmoking AN (14 F, 2 M, average age 25.06) and fourteen healthy controls (11 F, 3 M, average age 25.33) underwent [$^{18}$F]FEPPA PET scanning with concurrent arterial sampling. A two-tissue compartment model was applied to measure TSPO $V_T$.
Results: There was an interaction between group and the a priori selected regions, indicating that some regions were more different between groups than others (rmANOVA, $p = 0.013$). ANOVAs comparing individual regions between groups found greater TSPO $V_T$ in ACC (40% difference, $F_{1,26} = 12.03$, $p = 0.02$), thalamus (46% difference, $F_{1,26} = 8.86$, $p = 0.006$), dorsal putamen (31%, $F_{1,26} = 14.22$, $p=0.001$), ventral striatum (37% difference, $F_{1,26} = 6.89$, $p = 0.014$), and insula (26% difference, $F_{1,26} = 6.21$, $p = 0.019$).
Conclusions: To our knowledge, this is the first investigation of gliosis in AN. Differences in TSPO $V_T$ are most prominent in the ACC and thalamus, which is strong evidence of gliosis in these brain regions. This suggests that anti-inflammatory approaches should be considered for development as treatment in AN, and that these two regions should be investigated further for evidence of inflammation and injury in AN.

6. **Striatal dopamine release and hemodynamic response to fear conditioning in humans: a simultaneous [11C]Raclopride PET and fMRI Study**

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Introduction: In contrast to animals, evidence supporting a role for dopamine release in human fear conditioning is scarce due to methodological limitations. The objective of this study was to examine if dopamine release occurs during fear conditioning in humans using simultaneous [11C]raclopride positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).
Methods: We included 14 healthy participants in this preliminary analysis. Each participant underwent 2 simultaneous [11C]raclopride PET and fMRI scans, one during a baseline and another during a fear conditioning task. In addition, skin conductance was measured during the task and recall was measured immediately after, and one day after the task. The % change in the non-displaceable binding potential (?BPND) of [11C]raclopride to D2/3 receptors and the fMRI responses to fearful stimuli (CS+) versus neutral stimuli (CS-) were estimated.
Results: Participants conditioned towards the CS+ relative to the CS- as indicated by trending skin conductance responses (dependent-samples t-test, $t(13) = 1.48$, $p = 0.08$, one-sided) and successful recall right after the fear conditioning task and one day later (Wilcoxon signed-rank test, $W = 105$, $p$'s $< 0.0001$, one-sided). In a voxel-wise analysis, a significant cluster of [11C]raclopride ?BPND was detected in the right putamen ($p = 0.05$, uncorrected) that exclusively overlapped with the positive fMRI response to CS+ versus CS-.

Conclusions: Following fear conditioning, [11C]raclopride binding to D2/3 receptors decreased in the right putamen and overlapped with a positive fMRI response to CS+ relative to CS-. Our analysis indicates dopamine release in the putamen may facilitate optimal fear learning, and further data collection will support this preliminary relationship. Furthermore, fear learning is a process which is impaired in psychiatric populations. Future data collection in high-risk and psychiatric populations may reveal an abnormal relationship between dopamine and fear learning.

7. **Adrenergic A2-receptor agonism within the locus coeruleus attenuates two forms of learning driven by negative prediction error**

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Introduction: Refining previous learning when environmental contingencies change is a critical adaptive function. Current investigations have shown that systemic noradrenaline (NA) manipulations, as well as optogenetic manipulations of the locus coeruleus (LC), the primary source of forebrain NA, can modulate extinction learning, a paradigm in which subjects learn to stop responding to a previously rewarded cue.
Methods: To determine whether the contribution of NA is specific to extinction or extends to other forms of learning driven by negative prediction error (where reward is less than expected), we administered clonidine, an A2-receptor agonist which suppresses activity of LC-NA cells, directly to the LC prior to sessions where a negative prediction error was introduced. We compared the effects of clonidine in two tasks: a compound extinction task, where two previously rewarded cues are paired and no longer rewarded, and an overexpectation task, where animals are presented with two previously rewarded cues but receive a single reward rather than the expected two.
Results: In compound extinction, we found no differences between groups in training, extinction, or a spontaneous recovery test. However, animals that received clonidine reacquired responding to the compound extinguished cue significantly faster than saline animals, suggesting weakened extinction learning. In overexpectation testing, the saline group responded significantly less to a stimulus that had undergone overexpectation relative to a control stimulus, indicating that they had recalibrated their estimation of reward magnitude following training where reward was less than expected. In contrast, clonidine-treated animals did not differ in responding to the overexpectation versus control stimuli, suggesting that clonidine impaired learning resulting from overexpectation.
Conclusions: These results implicate the LC and its noradrenergic efferents in two learning paradigms where animals learn to reduce responding when reward is less than expected based on previous experience. Future investigations should identify the role of specific LC projections.

8. **Comparison of male and female avoidance, darting, And freezing behavior within the SPS model**

Donna Wood, Bailey Collins, Matt Biddle, Negin Mohammadmirzaei. Michelle Barth, Sushma Boyapati, Celine Jeun, Dayan Knox

Post-traumatic stress disorder (PTSD) is more likely to develop in women compared to men after trauma exposure. However, the sex differences in symptom manifestation are not well understood. The goal of this study was to use the single prolonged stress (SPS) rodent paradigm of traumatic stress to identify the different persistent fear-like behavioral symptoms male vs. female rats manifest after exposure to a traumatic experience. In experiment 1 we used a cued escape paradigm to examine the effects of SPS on acquisition and extinction of freezing and escape induced by a CS-tone. In experiment 2 we used the inhibitory/passive avoidance paradigm to examine the effects of SPS on acquisition and extinction of freezing and avoidance induced by an

aversive context. In experiment 1, the behavior observed in this paradigm did not allow for comprehensive experiments and results were inconclusive. The results of experiment 2 suggested that when males can avoid an aversive context, SPS deficits in the retention of extinction is not observed. Avoidance and freezing during extinction testing were negatively correlated with high levels of avoidance being associated with low levels of freezing in control female rats. SPS/female rats exhibited higher avoidance with no concomitant decrease in freezing during extinction testing. These findings further suggest that males and females respond differently to traumatic stress. The results of this research further emphasize the need for determining if trauma leads to persistent fear via different circuits and behavioral mechanisms in males vs. females.

9. **Conjugated GLP-1 and estradiol treatment as a novel treatment for age-related cognitive decline**

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Introduction: Consuming a high-fat high-sugar (western) diet (WD), not only increases the risk of obesity, but also negatively impacts cognition. Middle age is an especially critical period for WD-intake on cognition, especially in females. Glucagon-like peptide-1 (GLP-1)-based treatments have emerged as effective diabetic and obesity drugs. They also reduce inflammation, increase neurogenesis, and improve cognition, at least in males. Sex hormones, like 17ß-estradiol (E2), increase GLP-1's satiating efficacy, decrease body weight and improve cognition in females. Conjugation of these hormones (GE2) reduces body weight by selectively targeting GLP-1 receptor-expressing cells, avoiding off-target effects of E2. Here we explored GE2 effects on brain health. Methods: Ten-month old male and female Sprague Dawley rats were fed WD or standard diet (SD) for 1 month followed by 1 month of diet + daily injections (GE2, GLP-1, E2, GLP-1+E2, control) culminating in fear conditioning training and testing (2 days). Blood glucose levels were measured 10 days after treatment. After behavioral testing the animals were euthanized and the brain was collected immediately. Each hemisphere was collected separately to allow for assessment of both neurogenesis (doublecortin; DCX) and levels of inflammatory and synaptic proteins. Blood and fat tissue were also collected (inguinal white adipose tissue, IWAT; gonadal white adipose tissue, GWAT; brown adipose tissue, BAT). Results: WD increased body weight, GWAT and IWAT in both sexes. However, WD only impaired cued fear conditioning in males and increased basal blood glucose in females. GE2 reduced body weight and GWAT, but not IWAT, in WD females and males. GE2 enhanced contextual fear conditioning in all groups, regardless of sex. Work is ongoing to investigate effects of GLP-1, E2 or GE2 on neurogenesis and inflammation. Conclusions: Findings suggest that E2 and GLP-1 reduce body weight and improve memory alone, together, and in conjugated form dependent on sex and diet. CIHR: PJT 148662 Swedish Research Council:2021-00220

10. **Hormone therapy, age of menopause, previous parity, and APOE genotype affect cognition in aging humans**

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Introduction: Parenthood has long-lasting effects on the brain, as past pregnancy can be associated with increased risk and earlier onset of Alzheimer's disease in females. Males show short-term brain changes and long-term changes in hormone levels with parenthood. Carrying of the APOE?4 allele confers an increased risk of sporadic Alzheimer's disease. This project investigates how parenthood, APOE status, and female-specific factors (such as the age of menopause, and hormone therapy use for menopause) can affect cognition in aging individuals.
Methods: Data collected by the Canadian Longitudinal Study of Aging on more than 30,000 people were processed and analyzed using 'Plink' and RStudio. Middle-aged and older individuals (aged 45-85) carried out several cognitive tests evaluating verbal recall, verbal fluency, and prospective memory.
Results: Preliminary analyses indicate that having ?4 children is associated with worse cognition across several domains. As expected, carrying 2 (but not 1) copies of the APOE ?4 allele is associated with reduced performance on verbal recall and prospective memory tests. Later age of menopause was also associated with better performance on the Stroop latency, mental alternation, and verbal recall tests. Conclusion: These results suggest that there is a long-lasting impact of having children on cognition in males and females. Funding: This study was funded by CIHR Catalyst grant to LAMG (ACD-170296) and 4YF to TAP.

**11. Functional neurobiology of neurokinin B expressing D1 neurons in the lateral stripe of the striatum**

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Introduction: The striatum is a brain region implicated in motor function, reward, and cognition. Medium spiny neurons (MSNs) constitute the main neurons of the striatum. These neurons were historically divided into two groups: dopamine 1 receptor (D1) neurons, which directly project to other brain regions or dopamine 2 receptor (D2) neurons, which indirectly project via pallidal neurons. This division is used to sort the functional roles of MSNs and is called the conventional dichotomy model. However, recent research suggests D1 and D2 MSNs have overlapping functions. Additionally, molecularly heterogenous MSN subpopulations have been discovered that complicate defining MSNs as binary D1 or D2. A D1 MSN subpopulation (NKB-D1-MSN), which contributes to this molecular heterogeneity, is distinct in its co-expression of neurokinin B, a peptide highly expressed in the lateral stripe of the striatum (LSS). Our study will use mice to challenge the conventional dichotomy model's oversimplification by characterizing and functionally exploring this newly described MSN subpopulation.
Methods: To locate NKB-D1-MSNs, multiplexed in situ hybridization and immunohistochemistry will be used. Projection targets will be evaluated through antegrade tracing of NKB-D1-MSNs using Tac2-IRES-Cre transgenic mice. For evaluating functionality, NKB-D1-MSNs will be depleted in the LSS of Tac2-IRES- Cre mice using intracranial injections of a Cre-activated caspase 3-expressing virus; control mice of the same transgenic strain will get a sham injection. For the role of D1, D1 will be knocked out in all NKB-D1-MSNs by crossing Tac2-IRES-Cre mice with D1 floxed mice; Tac2-IRES-Cre mice will serve as controls. Both groups will be subjected to locomotion, reward/aversion, and cognitive and emotion- related behavioural testing; which MSNs are hypothesized to regulate. Conclusion: Our results will help establish a novel model of striatal

functioning that improves on the incomplete conventional dichotomy model. More importantly, our study could help advance research in reward processing, which helps related fields like addiction and mental health. Reference list available upon request, omitted due to space constraints.

**12. Prevalence and motivations for cannabis use in a clinical sample of individuals with binge eating disorder**

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Introduction: The prevalence of cannabis use among Canadians has risen in recent years. Nevertheless, limited research exists on cannabis use characteristics in specific clinical populations, including individuals with binge eating disorder (BED). The current study investigates the prevalence, motivations, and cannabis use characteristics of individuals seeking treatment for BED.
Methods: 53 individuals with BED were recruited from the Eating Disorders Clinic at St. Joseph's Healthcare Hamilton. This pilot investigation examined self-report measures assessing the frequency and method of cannabis consumption, along with motives of cannabis use and smoking history through the Marijuana Motives Questionnaire and Marijuana Smoking History Questionnaire.
Results: Over 50% of the sample (n = 30) reported having ever used cannabis, with 34.0% of participants reporting non-regular (non-daily) use (n = 18). More than 1/5 of BED patients reported past regular (daily) cannabis use (n = 5; 9.4%) or current regular use (n = 7; 13.2%). The mean age of initial use across groups was 18.4 years. Among those reporting regular use, 41.7% reported no serious attempts to quit using cannabis (n = 5). Only 11.0% of users reported taking cannabis for medicinal purposes that were authorized by a medical doctor. The main methods of consumption were joints (n = 16) or ingestion (n = 8), with most cannabis use occurring in social environments (66.7%) as opposed to alone (33.3%). Individuals reporting current regular use endorsed coping and enhancement factors as their primary motivations for use.
Conclusions: Our findings provide insight into the prevalence and motivations of cannabis use among individuals with BED, with a subset of individuals with BED demonstrating regular and potentially problematic use. Although BED patients report hedonic and coping motives, more research is necessary to understand underlying motivational characteristics which may perpetuate problematic use, and the implications these findings pose for clinicians/treatment providers.

**13. The effects of an IL-1R antagonist in a rodent model of postpartum depression and offspring stress resiliency**

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Introduction: The greatest risk to develop first-time depression in a female's lifespan is during the postpartum. Increased inflammation and reduced neuroplasticity are seen in an animal model of postpartum depression (PPD). Serotonin reuptake inhibitors (SSRIS) remain a common treatment

for PPD, despite their low efficacy. SSRI inefficacy is associated with increased levels of hippocampal interleukin-1ß (IL-1ß). Moreover, children of mothers with PPD experience an increased risk of depression. We investigated whether blocking the IL-1 receptor (IL-1R) would increase SSRI efficacy to reverse depressive-like endophenotypes in a rat model of PPD. In this study, we also paralleled the effects of PPD in both dam and offspring through examining neuroinflammation, and passive coping behaviours.
Methods: In our rodent model of postpartum depression, high corticosterone (CORT) was administered during the postpartum period along with fluoxetine (FLX) and/or anakinra (KIN), an IL-1R antagonist. FLX efficacy was measured using the forced swim test (FST), and maternal care observations. All dams were euthanized to examine inflammation, and markers of neuroplasticity in the hippocampus. All offspring were aged to postnatal day 60 and underwent 10 days of chronic unpredictable stress (CUS).
Results: In the dams, CORT increased time spent immobile and FLX+KIN did not rescue it. However, FLX+KIN rescued the reduced neuroplasticity seen in response to chronic CORT. In the offspring, maternal CORT increased immobility in the FST and maternal FLX+KIN reduced immobility in the FST, but only in females. Furthermore, CUS coupled with maternal CORT exposure reduced immobility in the FST, indicating a possible stress inoculation from maternal CORT. Maternal CORT and stress altered immune signaling in the dams, and offspring in a sex-dependent manner.
Conclusions: These findings indicate that IL-1ß may serve as a potential target for increasing antidepressant efficacy in people with PPD and increase stress resiliency in children of mothers with PPD.

**14. The preclinical behavioural pharmacology of psilocybin in mice**

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Introduction: The serotoninergic psychedelic drug psilocybin (PSI) has gained attention as a potential treatment for depression, substance abuse, and anxiety disorders. These disorders are characterized in part by deficits in cognitive domains such as reward processing, attention, and cognitive flexibility. However, because few studies have investigated PSI's direct effects on these domains, knowledge of the behavioural pharmacology of psilocybin is incomplete. Methods: We first assessed how PSI affected unconditioned locomotor activity. We then evaluated effects of PSI on operant responding for food. Finally, we investigated PSI effects on the more complex continuous performance (CPT) and probabilistic reversal learning (PRL) tasks, which assess attention and cognitive flexibility respectively. For operant responding, mice learned to bar press for food on a random interval 60s (RI) schedule. In the CPT, mice were trained to distinguish between target and non-target visual stimuli for milkshake reward. In the PRL task, mice were trained to learn an action-reward contingency and flexibly adjust their behavior when previously learned reward-related contingencies were reversed. On each task once performance stabilized, mice were tested following injections of PSI (0, 0.3, 1, and 3 mg/kg). Results: PSI at 3 mg/kg reduced locomotor activity. In RI sessions, 1 and 3 mg/kg PSI reduced operant responding for food and increased the frequency of long duration pauses (>10 s) in responding. In the CPT, 3 mg/kg reduced hit rates, and induced conservative responding (less likely to respond). In the PRL, PSI did not affect the ability to successfully adapt to reward contingency reversals. Conclusions: PSI may affect performance on a test of visual attention and on operant responding for food,

though this may in part be due to drug-induced locomotor deficits and/or time-perception changes. Future work is required to investigate PSI's effects on more demanding tasks or following repeated PSI exposure.

**15. Maternal corticosterone dampens fear expression in male and female adult offspring during negative cognitive bias task**

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Introduction: Cognitive symptoms of major depressive disorder (MDD), such as negative cognitive bias (NCB), are resistant to treatment and understudied. NCB is the interpretation of ambiguous stimuli as negative. Up to 20% of females develop postpartum depression (PPD), which increases the risk of their children developing MDD later in life. MDD is associated with aberrant neural activity in the dorsal and ventral hippocampus (dHPC & vHPC) and amygdala (AMYG). Pilot data in rats indicate that despite similar levels of NCB, chronic stress-induced alterations to neural activity in the vHPC, dHPC, and AMYG are sex-specific. In this study, we examined the effects of a rodent model of PPD on NCB and underlying neurobiology in offspring. Methods: We exposed rat dams to high corticosterone (CORT) for 21d postpartum and tested for NCB in their adult offspring (postnatal day 60). To model cognitive bias, we trained rats to discriminate between shocked context A and non-shocked context B for 16d. Rats were then tested in ambiguous context C (mix of A & B); higher freezing indicates NCB. Finally, we used multiplex in situ hybridization (mFISH) to characterize the neuronal subtypes activated during cognitive bias in the dHPC, vHPC, and AMYG. Results & Conclusions: Maternal CORT-treated offspring exhibited less freezing across contexts than controls, suggesting maternal CORT dampened fear behavior. Furthermore, there was a sex difference among maternal CORT-treated offspring whereby males displayed more NCB than females, suggesting a greater dampening effect in females than males. We propose that maternal CORT exposure may act as a primer, inoculating offspring against expression of fear behavior during the NCB task. mFISH data analysis is ongoing, but we expect to find region-specific effects of sex and maternal treatment on neural activation. This research will help elucidate possible mechanisms by which early maternal treatment affects cognitive bias in offspring.

**16. Modulation of the anxiolytic effects of cis-resveratrol by cap-dependent translation**

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Introduction: Resveratrol (RSV) is a phenolic compound found in many plant and plant products, and it exists as cis (cis-RSV) and trans (trans-RSV) isoforms, with trans-RSV being the most abundant. Recently, RSV has been proposed as a potential treatment for mood disorders. In animal models, RSV decreased immobility time in the forced swim test (FST), increased exploration of the center of the open field (OF) and open arms of the elevated plus maze. Recently it was shown that trans-RSV is neurotoxic, but cis-RSV is neuroprotective and increases de novo protein synthesis through the mammalian target of rapamycin 1 (mTORC1) pathway in cultured neurons, suggesting that the therapeutic effect is restricted to the cis isoform. Methods: Male (n=48) and female (n=26) adult (P60+) mice were given 14 daily injections of cis-RSV (IP, 10 mg/kg) or vehicle (IP, 2% EtOH in 1x PBS). On the 14th day, mice underwent the OF 1 hour post injection. Following an hour rest period, mice then were placed in the FST. Results: We found that male WT mice treated with cis-RSV had increased exploration of the center of the OF (111.80 ?

21.42s) compared to the saline treated group (39.01 ? 6.59s), without altering general locomotion. Further, the effects on exploration of the center of the OF were absent in mice mutant for an mTORC1 effector on translation. In contrast, there was no effect of treatment in female mice (85.56 ? 9.96s) compared to vehicle treated counterparts (108.73 ? 19.94s). cis-RSV did not affect immobility in the FST in any strain of male and female mice. Conclusion: The differential effects seen in the open field task suggest a sex specific effect of cis-RSV on measures linked to anxiety. The lack of effects in the mutant mice demonstrate that the effects of cis-RSV are dependent on mRNA translation.

### 17. Paroxetine administration during pregnancy resulted in autistic-like behavior in offspring

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Introduction: The utilization of antidepressants during pregnancy has witnessed a significant rise over the years, with selective serotonin reuptake inhibitors (SSRIs) being the most commonly prescribed class. Recent epidemiological research has indicated an escalated risk of autistic spectrum disorder (ASD) in children born to mothers treated with SSRIs during pregnancy. To delve into this matter, we conducted an investigation focusing on the long-term consequences of gestational paroxetine exposure in mice.
Methods: Female C57BL/6 mice were randomly assigned to either the paroxetine hydrochloride (PRX) treatment group, receiving PRX in their drinking water (10 mg/kg), or the control group, receiving regular water. The treatment commenced on the first day after mating and ended after parturition. We assessed the maternal behavior of the dams and their offspring, including anxiety, locomotion, sociability, repetitive and obsessive-compulsive behaviors. Additionally, a separate cohort of litters was cross-fostered between control and treated dams to control for the potential effect of alterations in maternal behavior.
Results: Our findings indicate that chronic PRX treatment impaired the dams' maternal behavior and induced behavioral alterations associated with ASD in the offspring, with a more pronounced effect observed in males compared to females. Specifically, the mice exposed to SSRIs during gestation displayed deficits in vocalizations, sociability, and social novelty recognition, along with an increase in repetitive/stereotypic behavior. Nevertheless, assessments of anxiety-like and locomotor behavior did not reveal any differences, indicating normal anxiety levels, motor function, and motor learning. It is noteworthy that cross-fostering did not lead to changes in the behavior of the offspring, thereby emphasizing the lesser role of maternal behavior in this context. Conclusion: Our data unveil that gestational paroxetine exposure results in multiple behavioral deficits, and it indicates that the effects of gestational paroxetine exposure alone suffice to induce ASD-like deficits.

### 18. Fatty acid amide hydrolase in major depressive episodes: a [11C]CURB positron emission tomography study

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Introduction: There is a growing interest in the endocannabinoid system (ECS) as an alternative signaling pathway to treat symptoms of major depressive disorder (MDD), and preclinical evidence suggests that the density of fatty acid amide hydrolase (FAAH), an ECS enzyme, is elevated within fronto-limbic brain regions in depressive models. Our aim was to characterize the ECS in humans with MDD using positron emission tomography (PET), and we hypothesized that [11C]CURB lambda-k3, an index of FAAH density, would be elevated in the prefrontal cortex (PFC), hippocampus, and anterior cingulate cortex (ACC) in MDD patients compared to healthy controls.
Methods: [11C]CURB lambda-k3 was measured using PET in 15 unmedicated MDD cases and 15 age- and sex-matched healthy controls, aged 18 to 65. All psychiatric participants had a primary diagnosis of MDD and met criteria for a current major depressive episode on the Structured Clinical Interview for DSM-5-Research Version. There were 11 females in each group. The Beck Depression Inventory and Marin Apathy Evaluation Scale (MAES) were administered for exploratory correlational analyses.
Results: No significant differences in [11C]CURB lambda-k3 were observed between MDD patients and controls (linear mixed effects model; PFC, $F_{1,34}=0.010$, $p=0.992$; ACC, $F_{1,34}=0.461$, $p=0.502$; hippocampus, $F_{1,34}=1.017$, $p=0.320$). However, exploratory analyses revealed a significant positive correlation between MAES scores and FAAH binding in the medial PFC ($r=0.673$, $p=0.012$), ventrolateral PFC ($r=0.586$, $p=0.035$), and amygdala ($r=0.660$, $p=0.014$) amongst MDD patients. Conclusion: Our study is the first to investigate FAAH in MDD using [11C]CURB PET. Our exploratory analyses suggest that fronto-limbic FAAH might be related to apathetic behaviour in MDD, which is relevant because a diminution of motivation and goal-directed behaviour is a core feature of the disorder. Upon further investigation, FAAH inhibitor therapeutics might be considered for MDD cases with greater apathy.

### 19. Intracortical myelin in bipolar disorder type 1 and the impacts of neuregulin-1 variation and age

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Introduction: Bipolar disorder is associated with cortical abnormalities, including deficits in intracortical myelination. Intracortical myelin follows an inverted-U trajectory over the lifetime, but this trajectory is blunted in individuals with bipolar disorder. Little is understood about which genetic factors contribute to these deficits. Neuregulin-1, a cell-signalling protein, has been shown to contribute to cortical abnormalities and increase susceptibility to various disorders. Assessing the prevalence of neuregulin-1 polymorphisms, notably rs6994992, in bipolar disorder may elucidate the genetic contributors of intracortical myelin deficits and increase our understanding of factors causing susceptibility to bipolar disorder.
Methods: 67 participants with bipolar disorder type 1 and 75 healthy control participants were recruited. T1-weighted MRI images were collected and processed for R1 signal intensity, a proxy measure of intracortical myelin. Blood samples were genotyped at the rs6994992 locus. Linear models were used to test whether intracortical myelin can be predicted by age, bipolar diagnosis and NRG1 genotype.
Results: Intracortical myelin is significantly predicted by age, diagnosis and genotype together in the bilateral motor cortex (left: $R2 = 0.09$, $p < 0.01$, right: $R2 = 0.06$, $p < 0.05$), the right premotor cortex ($R2 = 0.095$, $p < 0.001$), and the right inferior frontal cortex ($R2 = 0.098$, $p < 0.001$). Age is

a significant predictor of intracortical myelin in the right dorsal anterior cingulate cortex ($p < 0.05$, ?p2 = 0.029), the bilateral motor cortex (left: $p < 0.001$, ?p2 = 0.091, right: $p < 0.05$, ?p2 = 0.043), the right premotor cortex ($p < 0.05$, ?p2 = 0.086), and the right inferior frontal cortex ($p < 0.05$, ?p2 = 0.07).
Conclusions: Our study suggests that the inferior frontal, premotor and primary motor cortices may be regions of interest for understanding how intracortical myelin changes throughout the lifetime, especially in bipolar disorder.

**20. Effects of adversity on brain function: evidence from a multilevel kernel density analysis (MKDA) of fMRI studies**

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Introduction: Exposure to adverse life experiences has been proposed to increase the risk for mental health problems by altering mesocorticolimbic responses to psychological challenges. However, despite compelling evidence in laboratory animals, studies in humans have yielded variable results. Indeed, a recent activation likelihood estimation (ALE) meta-analysis failed to identify consistent effects of adversity on brain function. To address these issues, we conducted a multilevel kernel density analysis (MKDA) meta-analysis, an approach considered more robust than ALE to small sample sizes and methodological differences between studies. Among other features, the MKDA approach can evaluate the consistency of activations in neural regions across different challenges and the specificity of neural activations associated with a particular psychological process.
Methods: A literature search was conducted using four databases: PsycINFO, Medline, EMBASE, and Web of Science. Eighty-three fMRI studies were included yielding a combined sample of 5242 participants and 801 coordinates.
Results: Prior adversity exposure was consistently linked with heightened amygdala reactivity (FWER corrected at $p < .001$; $x = 22$; $y = -4$; $z = -17$) and blunted prefrontal cortex activity (FWER corrected at $p < .001$; $x = -39$; $y = 16$; $z = -8$), particularly during emotion processing task and in individuals exposed to severe trauma.
Conclusions: These MKDA-derived results provide the clearest evidence to date that prior adversity produces long-lasting alterations in brain reactivity to diverse challenges. Together, heightened amygdalar reactivity and diminished cortical reactivity might decrease the ability to cope with later stressors, producing enduring susceptibility to diverse mental health problems.

**21. Social behaviour and ultrasonic vocalizations: creating a new model of nicotine withdrawal**

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Introduction: Nicotine withdrawal represents a major obstacle to smoking cessation, but the standard rodent model of nicotine withdrawal is problematic. First, it relies on continuous (minipump-delivered) administration of high-dose nicotine that produces plasma levels far exceeding those found in typical smokers. Second, during chronic nicotine exposure, a nicotinic antagonist reliably precipitates an acute opioid-like withdrawal syndrome, not seen in smokers. We therefore sought to identify signs of nicotine withdrawal of more relevance to smoking, by using intermittent low-dose exposure and by focusing on smoking-relevant signs/symptoms, specifically irritability, agitation, anxiety, and negative affect.
Methods: Rats were given chronic forced-choice nicotine via their drinking water over 3 weeks at 3

doses (0, 0.02, or 0.05 mg/ml, all in a 1% saccharin solution), and then all groups were switched to water alone. At the end of chronic administration, and over 7 days of withdrawal, the rats' behaviour was assessed while they engaged in a socially challenging task in an unfamiliar social interaction. We analyzed video-recorded behaviors indicative of irritability, anxiety, or distress, and affect-associated ultrasonic vocalizations (USVs).
Results: Daily nicotine intake was considerably lower than in the standard minipump-based procedure. Rats became markedly more aggressive in the early post-withdrawal period, after the higher nicotine dose; this withdrawal sign dissipated by day 7. In contrast, no withdrawal-associated changes were detected in several other social and non-social behaviours, and in 50-kHz call rate and call subtype profile. Conclusion: After adult rats had chronically consumed nicotine at a dose predicted to produce smoking-relevant plasma levels, they showed a selective increase in aggressive behaviour, reminiscent of the irritability seen during smoking cessation. It this finding is replicated, it may ultimately be possible to replace the standard, but highly questionable, nicotine withdrawal model. Acknowledgements: Canadian Institutes of Health Research

### 22. Parity and APOEe4 genotype influence recruitment of the hippocampus in response to a cognitive task

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Introduction: Females have a higher lifetime risk of Alzheimer's disease (AD) and show greater neuropathology and cognitive decline than males. To better understand how AD affects females, this study explored the long-term influences of previous parity (pregnancy and motherhood) on AD endophenotypes in middle-aged female rats. We hypothesized that the effects of parity would depend on Apolipoprotein (APOE) e4 status, the greatest genetic risk factor for late-onset sporadic AD, as APOEe4 genotype confers a greater risk and burden of AD in females than males. Female-specific factors like parity are important to consider, particularly in AD research, because previous parity is associated with increased risk, more severe neuropathology, and earlier age of onset for AD. Further, neurogenesis, the production of new neurons in the brain, has been shown to decline with AD severity as well as APOEe4 genotype, but there is limited research on how previous parity may contribute to this relationship. As such, this study investigates the impact of previous parity and APOEe4 genotype on spatial working memory and neurogenesis in middle-aged rats.
Methods: We used a sporadic AD rat model that expresses humanized (h)APOEe4. Wildtype and hAPOEe4 rats were either nulliparous (never mothered) or primiparous (one-time mothers). Rats were tested on a spatial working memory task at middle age (13-14 months old), then euthanized to examine markers of neurogenesis.
Results: We found that primiparous hAPOEe4 rats increased use of a non-spatial strategy in the cognitive task and had fewer and less active new-born neurons in the dentate gyrus of the

hippocampus. Conclusion: Together, these findings suggest that primiparous hAPOEe4 rats may be recruiting different features of the hippocampus or other brain regions during spatial working memory retrieval and underscore the importance of considering genotype and female-specific factors like reproductive history in aging and AD research.

**23. Developmental change in human substantia nigra: preliminary observations early and late in life assessed with neuromelanin-sensitive MRI**

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Neuromelanin-sensitive MRI (NM-MRI) has been applied to assay integrity and function of human catecholamine systems in vivo. To optimize NM-MRI use, it is important to account for the known neuromelanin (NM) accumulation in the substantia nigra (SN) throughout the lifespan. NM-MRI images were collected at two locations using the same turbo spin echo sequence. Sample 1 included individuals aged from 7-30 years (n=42) and from 52-82 years (n=26). Sample 2 included individuals over 52 years old who had longitudinal data with 1-2 annual follow-up scans (n=68). In sample 1, the younger group showed significant signal increase with age, and voxelwise analysis found a large set of voxels within central SN where the signal increased with age, while almost no SN voxels showed decreasing signal. In older individuals, 312 voxels in central SN showed increasing signal with age and 178 voxels in peripheral SN showed decreasing signal with age. When examining longitudinal SN signal change in sample 2, a large cluster of voxels showed decreasing signal over time and a small cluster showed increasing signal over time. Examining spatial overlap between SN voxels where the signal changed with age (Sample 1, older group) and those where the signal changed over time (Sample 2) showed significantly more overlap than would be expected by change for both increasing and decreasing signal voxels. In the future, we will investigate the impact of clinical and demographic factors in an expanded and longitudinal sample to optimize the potential for NM-MRI to be used as a biomarker.

**24. D1 and D2 receptor activity determines the valence of ventral striatal dopamine**

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Introduction: Dopaminergic inputs to the ventral striatum robustly support self-stimulation behaviour. Elevations in ventral striatal dopamine have diverse actions on downstream substrates expressing dopamine type-1 (D1) and type-2 (D2) receptors and the contribution of these substrates to the valence of ventral striatal dopamine is unclear.
Methods: To uncover the role of neurotransmission at D1 and D2 receptors in determining the valence of ventral striatal dopamine activity we developed a novel self-stimulation procedure in which mice are trained to hold-down a lever to continuously photostimulate ventral striatal dopamine fibers.
Results: As the stimulation frequency increased (2.5, 10, 40 Hz) mice spent more cumulative time holding the lever down to receive stimulation but did so by performing more frequent hold-downs of briefer mean duration. The divergence of cumulative and mean hold-down duration suggests there may be an aversive component to high-frequency ventral striatal dopamine stimulation which mice mitigate by disengaging the lever. Pharmacological modulation of neurotransmission at D1 and D2 receptors produced frequency-dependent changes in mean, but not cumulative, hold-down duration. Specifically, the D1 agonist SKF 38393 reduced, whereas the D2 antagonist raclopride elevated, mean hold-down duration – this effect was most pronounced at low to moderate (2.5, 10 Hz) stimulation frequencies. Neither the D1 antagonist SCH23390 nor the D2

agonist Quinpirole affected mean hold-down duration. SKF38393 and Quinpirole, but not Raclopride or SCH23390, reduced cumulative hold-down duration irrespective of stimulation frequency. No treatment affected the number of hold-downs performed. Conclusion: Increasing neurotransmission at D1 and D2 receptors modulates the mean duration of self-stimulation hold-downs, consistent with the amplifying the negative and positively valenced components of ventral striatal dopamine activity. The capacity for ventral striatal dopamine to support self-stimulation depends critically on neurotransmission at D1 and D2 receptors. Targeting dopamine D1 receptors to treat psychopathologies characterized by a failure to disengage behaviour may be efficacious.

**25. Predicting anxiety onset with machine learning using the Canadian Longitudinal Study of Aging (CLSA)**

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Introduction: Anxiety disorders are one of the most frequent and costly mental illnesses among the ageing population. Currently, anxiety poses a significant burden globally, as it accounts for ~8 Disability Adjusted Life-Years (DALYs) in the adult population in comparison to ~17 DALYs in the ageing population (45 years and up). Because of the burden anxiety poses on the ageing population, we must develop tools to identify the risk factors behind anxiety onset. One such tool is machine learning (ML), an artificial intelligence tool that can learn patterns within the data to form a prediction.
Methods: To develop our prediction of anxiety onset, we applied ML to use the Canadian Longitudinal Study of Ageing (CLSA) data set, a study with individuals ranging from 45 to 85 years old. To define future anxiety onset, we identified 714 individuals that did not have anxiety at baseline in 2015, but developed anxiety in 2018 at follow-up. We inputted the baseline data into an imbalanced random forest algorithm to make a prediction on anxiety onset.
Results: We were able to achieve an area under the curve (AUC) of 81.4% using our model. An AUC was used to measure the performance of our ML model, where an AUC of 50% means the model was not able to distinguish between anxiety onset and non-anxiety onset individuals. Furthermore, we identified high frailty, past depression and/or mood disorder diagnosis, and anxious personality traits, as predictors of future anxiety onset. Hence, we also investigated whether depression related variable alone can be used to predict anxiety onset. We determined that depression-related variables along could not reliably predict anxiety onset (AUC of 69.8%).
Conclusion: Thus, our research demonstrates the potential of ML in creating personalized prediction models using for identifying anxiety onset among middle-aged and older adults.

**26. Association study of immune gene candidate, complement component C4, and suicide risk in schizophrenia**

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Background: Suicide is a major cause of death among schizophrenia patients, with approximately 50% attempting and 10% dying from suicide. The complement component C4 gene, an immune gene involved in the innate immune system, has been identified to be strongly associated with schizophrenia risk. In addition, preliminary findings show that the C4 gene has also been associated with suicide risk. The C4 gene has a complex genetic structure, with four possible forms: C4AL, C4BL, C4AS, and C4BS. The purpose of this research is to investigate the

relationship between the C4 variants and suicide risk in patients with schizophrenia, and potentially identify a new genetic marker for suicide risk in this group. With C4AL having the highest association with increased schizophrenia risk, it is hypothesized that patients with C4AL will have an increased suicide risk than those without.
Methods: This study will include a sample of N=434 schizophrenia patients (311 males:123 females) from our ongoing study on the genetics of schizophrenia. DNA extractions have been performed from blood samples. The precise C4 gene variant and the number of repeats are determined using PCR and custom genotyping assays. Data on suicide attempts, suicidal ideation, and suicidal plans are extracted from the mood disorder module of the SCID and summary of medical records.
Results: Logistic regression analyses showed a significant negative association between the C4AS variant and suicide attempt (p=0.036, OR=0.457)/suicidal ideation (p=0.045, OR=0.565). Further sex-stratified analyses revealed that this association is stronger in males compared to females.
Discussion and Conclusion: This study is the first of its kind to analyze the association between the complement component C4 gene and suicide risk. Based on our results, the presence of the C4AS variant in schizophrenia patients may have a protective role against suicide attempt/ideation. Further investigation with larger sample sizes may clarify these results.

**27. Exploring genetic biomarkers in the Wnt signaling pathway for bipolar disorder: insights and implications**

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Introduction: The Wnt signaling pathway has garnered significant attention in psychiatric research due to its vital role in neurodevelopment. Understanding the potential involvement of the Wnt signaling pathway in bipolar disorder may offer valuable insights into the underlying mechanisms of this complex psychiatric condition.
Methods: In this study, 205 bipolar patients and 205 matched healthy controls were recruited. DNA was extracted from blood. The tetra-ARMS primer PCR was used for genotyping 15 variants from 9 genes. Obtained results were confirmed by sequencing. The identified genetic variants were investigated using bioinformatics tools to assess their potential implications in neuronal function.
Results: The findings of the study revealed associations between genetic variants of *MARK2*, *BDNF*, *GSK3B*, *PPARD*, and *ADCY2* genes and certain aspects of bipolar disorder. The MARK2 rs10792421 showed an association with treatment response to lithium (p = 0.028), indicating its potential as a biomarker for predicting treatment outcomes. The *BDNF* Val66Met variant exhibited associations with bipolar susceptibility, suicidal behavior, and response to lithium treatment. The *GSK3B* rs334558 variant was found to be associated with patients' response to lithium treatment (p= 0.16), while the *PPARD* rs2267665 variant showed an association with bipolar disorder susceptibility (p=0.009). The study also identified *ADCY2* rs2290910 as a potential biomarker for bipolar disorder risk (p = 0.001), suicide tendency (p = 0.004), and response to lithium therapy (p = 0.001), particularly in the female population. In-silico analysis using tools such as Haploreg revealed potential regulatory elements and predicted their involvement in neuronal networks.
Conclusion: This preliminary study suggests the importance of genetic biomarkers involved in neuronal pathways in bipolar disorder and related behaviours. The identification of biomarkers can contribute to personalized treatment approaches and improved management of bipolar disorder. Further research is warranted to validate these findings and explore the underlying mechanisms of these genetic associations.

### 28. Investigating the genetic linkage of heart rate variability (HRV) and anxiety disorders: polygenic risk score overlap and replication of HRV genome-wide polymorphisms in individuals with anxiety disorders

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Introduction: Anxiety disorders are associated with reduced heart rate variability (HRV), a heritable measure of difference in time between heartbeats. This study examined the genetic overlap between anxiety risk and HRV using polygenic risk scores (PRS). In addition, polymorphisms related to HRV were investigated to determine if they influence anxiety risk, potentially mediated through different HRV levels.
Methods: In 184 Europeans (100 anxiety disorder, 84 controls, age 18-65, 69% female), we measured 5-minute resting HRV using the Empatica wristband and genotyped using Global Screening Array. Anxiety and HRV PRSs were computed using the summary statistics from a meta-analysis of anxiety disorder GWASs and meta-analysis of HRV GWASs, respectively, using a clumping and thresholding approach with standard p-value thresholds (5e-8 to 1) followed by high-resolution analysis (PRSice-2). To test for anxiety disorder PRS association with HRV in our sample, and an HRV PRS association with anxiety disorder, we used linear and logistic regression, respectively. Additionally, using the 15 significant polymorphisms from a pre-existing HRV GWAS, we performed mediation analyses to investigate their associations with anxiety disorder in our sample through resting HRV.
Results: The anxiety PRS explained 2.7% variance in HRV (p=0.029; p-value threshold of 0.0004, 501 SNPs). The HRV PRS explained 4.4% variance in anxiety (p=0.018; p-value threshold of 3.34e-05, 48 SNPs). Mediation analyses revealed that rs12980262 *NDUFA11* A-carriers and rs180238 and rs4262 *GNG11* C-carriers had higher anxiety risk through lower HRV (b=0.35, 95%CI=0.09–0.76; b=0.11, 95%CI=0.005–0.30; b=0.11, 95%CI=0.01–0.28).
Conclusions: This study demonstrates an anxiety-HRV genetic overlap, and the association of HRV-related genes to anxiety, with effects influenced by HRV. These variants have not been studied in the context of psychiatry and are therefore novel markers to explore further. This study thus supports HRV as a biomarker that may aid the search for genetic factors of anxiety.

### 29. The effect of weight loss on brain age in schizophrenia

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Introduction: Individuals with schizophrenia often have metabolic comorbidities, such as type 2 diabetes, and experience a reduced life expectancy due to cardiovascular diseases. Obesity, a common comorbidity in schizophrenia, can negatively affect brain health. However, there is limited understanding of how metabolic disorders impact brain structure in individuals with schizophrenia, and the effects of weight changes following pharmacological interventions have not been explored. In this study, we will investigate changes in brain morphology, specifically brain-age, in overweight or obese individuals with or without diabetes who have been diagnosed with schizophrenia. We will assess these changes before and after a 12-week period of pharmacological treatment targeting metabolic dysfunction.
Methods: This analysis includes 48 participants, aged 18 to 65, from three double-blind studies investigating interventions for antipsychotic-induced metabolic dysfunction: TAO study (NCT01794429, 9 on medication and 8 on placebo), Metformin for prediabetes/diabetes study (NCT02167620, 11 on medication and 8 on placebo), and Topiramate in clozapine study (NCT02808533, 12 on medication). We collected brain structural MRI, fasting lipids, and body mass index at baseline and week 12. We utilized a deep learning-based neuroradiology classifier that was trained and tested to estimate the brain age of each participant. The study aims to examine the changes in BMI and estimated brain age scores using baseline and endpoint data.
Results: The BMI change was found to be statistically significant in the whole sample ($p<0.001$), as well as in the medication group ($p=0.005$) and placebo group ($p=0.008$). There was a positive correlation between change in brain-age and BMI ($r=0.3$, $p=0.04$), with no significant difference in the strength of the correlation between the medication and placebo groups.
Conclusion: These results indicate a positive correlation between difference of weight loss and predicted brain age between baseline and endpoint, suggesting that weight can help decrease brain age.

### 30. Cigarette smoke extract and nicotine evoke similar interoceptive effects in an appetitive Pavlovian task in male and female rats

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Introduction: Although nicotine is the primary component of interest in tobacco, the other ~8000 constituents in cigarette smoke are thought to interact with nicotine to contribute to the pharmacological effects relevant to tobacco use disorder. Using a Pavlovian drug discrimination task, we hypothesized that rats could discriminate between nicotine and cigarette smoke extract (CSE) of the same nicotine concentration based on the presence of constituent chemicals.
Methods: Rats were assigned to one of three training conditions in which intermixed daily injections were administered before chamber placement. The interoceptive stimulus elicited by the injected compound indicated whether a light conditioned stimulus (CS) would, or would not, be followed by sucrose. Increased dipper entries during the CS indicated greater anticipation of impending sucrose. Groups included nicotine vs vehicle with nicotine signaling sucrose, CSE vs vehicle with CSE signaling sucrose, and CSE vs nicotine with CSE signaling sucrose. This final group determined whether rats could discriminate based on other constituents. Results: Subjects readily discriminated between nicotine and vehicle and between CSE and vehicle within ~20 training sessions; however, they were unable to discriminate between CSE and nicotine after 72

sessions. Conclusions: Our results confirm that CSE is a successful Pavlovian discriminative stimulus and adds to previous nicotine literature. Interestingly, we demonstrate that CSE and nicotine do not create distinct interoceptive environments under current training conditions. Significance: Nicotine has long been used as a proxy for tobacco in non-human animal studies. However, there has always been an undercurrent regarding the appropriateness of this approach given the myriad constituents in tobacco. Though generalization to other behavioural preparations must be done with extreme caution, the current findings suggest that, at least in some capacity, there is overlap in the stimulus characteristics of nicotine and CSE.

### 31. Investigation of complement *C4* gene and schizophrenia phenotypes

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Background: The most recent GWAS identified 287 loci to be associated with schizophrenia, in which the complement *C4* gene is still the strongest genetic biomarker for schizophrenia risk. The *C4* gene codes for two different isotypes, *C4A* and *C4B* with long or short forms (C4L & C4S). Studies showed that the brain expression of C4 depends on its structural forms and C4L is associated with higher *C4A* brain expression. We aimed to investigate the association between *C4* and treatment-resistant schizophrenia (TRS), the number of hospitalization (NOH), GAF score, symptom severity and age of onset.
Methods: The total of 613 subjects, over the age of 18 were included in this study. The data were retrospectively extracted from the Toronto Schizophrenia study. Patients prescribed clozapine were considered treatment resistant.
Results: Our results showed that patients hospitalized for 2 or more times, had significantly lower copy numbers of *C4S* (p = 0.023) and *C4AS* (p=0.007). In sex-stratified analysis only, there was a significant negative association between *C4S* and TRS in males (p= 0.047). Moreover, we found that age of onset was associated with higher *C4AS* (p = 0.050), and symptom severity was associated with higher copy numbers of *C4B* (p = 0.010) and *C4B* expression (p = 0.011). Also, *C4A* (p = 0.015) and *C4A* expression (p = 0.012) had significant positive association with GAF scores.
Conclusion: Our results support the sex effect of *C4* risk in schizophrenia and suggest that *C4S* may have a protective effect and that *C4B* might be involved in the more severe forms of schizophrenia. While our study provides further evidence for the *C4* gene as a genetic biomarker in schizophrenia risk, it encourages future investigations in exploring the role of *C4* in other schizophrenia-related characteristics such as antipsychotic response and suicide.
Schizophrenia, Complement C4 gene, Treatment Resistance Schizophrenia

### 32. Sex differences in a stress induced depressive phenotype: a time course of behavioural and central effects

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Introduction: One in four people in North America will be diagnosed with an anxiety or mood disorder, making these the most prevalent psychiatric illnesses. Females show a two-fold increase in the prevalence of mood and anxiety disorders and there are similar sex differences in cognitive, depressive, and anxiety behaviours following exposure to acute and chronic stressors in rodents. The relationship between stress and depressive-like phenotypes in rodents has been documented across various stress models with noted sex differences in depressive-like phenotypes. However, many of these studies show inconsistent results and have employed different stress models for varying durations. Therefore, a systematic study of sex differences in the response to chronic stress over time is lacking. We have previously shown that astroglial cells respond to five weeks of chronic stress by upregulating perineuronal net (PNN) components, accompanied by upregulation of PNNs surrounding interneurons in the PFC. However, it is unknown what duration of chronic stress is needed to induce these changes or whether there are sex differences in their onset or trajectory.
Methods: We employed a rodent model of chronic variable stress (CVS) whereby male and female mice were exposed to a time course of chronic stress ranging from one to five weeks in duration followed by a battery of behavioural testing to assess depressive and anxiety-like behaviours.
Results: We found a significant effect of stress on emotive behaviours as early as one-week post-stress onset in males and by two weeks both sexes showed similar stress-induced phenotypes compared to controls. Preliminary results suggest that microglia show activation as early as one-week post-stress in males and that interneuron expression of perineuronal nets initially decreases and later increases with continued stress exposure.
Conclusion: Altogether, these data show sex differences in behavioural and cellular patterns of response to chronic stress over time.

### 33. Epigenome-wide association study of improvement in depressive symptoms across psychiatric disorders following naturalistic treatment

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Introduction: Epigenetic modifications are known to significantly impact the relationship between genes and the environment and play an important role in many complex diseases, including psychiatric disorders. Epigenome-wide association studies (EWAS) examining medication treatment outcomes in psychiatry specifically are very limited, although research in depression is promising. Thus, we conducted an EWAS to discover novel peripheral DNA methylation biomarkers potentially associated with improvement in the depressive symptoms that occur across psychiatric disorders.
Methods: A subset of individuals scoring 20 or higher on the Beck Depression Inventory (BDI) (n=187, age 18-65, 128 female), were derived from our naturalistically treated Toronto CAMH IMPACT study. Patients were referred for pharmacogenetic testing if they had not responded, or were intolerant to, at least one psychotropic medication. Methylation was interrogated using the HM450 array. Change in BDI score was used to measure depressive symptom improvement over eight weeks. The relationship between methylation levels and change in BDI score was then investigated using linear modelling.
Results: The average percent change in BDI score following eight weeks of naturalistic treatment was -23.05 ± 36.16. Our most significant results identified DNA methylation patterns of 10 CpG probes located within 8 genes (*C8orf71, SYT6, SLK, CNP, ZNF747, HSD17B4, TMEM50B,*

*TMEM223*) that were nominally associated with change in depression (BDI) scores. No probe was significant after correction for multiple testing (threshold $p < 10^{-7}$). Increased DNA methylation for our top hit, cg04315200, located at Chr2:3888395 and not near a known gene, was nominally associated with impaired treatment response ($\beta = 17.43$, $p = 4.27x10^{-5}$).
Conclusion: Our preliminary pharmaco-epigenetic EWAS analysis suggests that DNA methylation may be involved in change of depression symptoms during treatment across psychiatric disorders. Future work will include gene set enrichment and risk score analyses, in addition to a predictive machine-learning approach, in a larger data set.
Keywords: pharmacogenetics, methylation, psychiatry, depression, antidepressant treatment response

**34. Optogenetic stimulation of astroglia prevents dopamine neuron degeneration**
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Astrocytes are a heterogenous glial cell type that are intimately involved in several critical functions including the modulation of ion homeostasis, the regulation of oxidative stress and the production of key energy substrates for neurons. They are essential in injury and disease response through morphological, physiological and functional changes. Given this, it is unsurprising that astrocyte dysfunction is observed in Parkinson's disease (PD). For example, the overexpression of α-synuclein specifically in astrocytes is sufficient to produce severe motor deficits.[1] Furthermore, the selective targeting and stimulation of astroglia using optogenetics has been shown to stimulate the release of FGF2 and increase functional repair following administration of MPTP and 6-hydroxydopamine (6-OHDA)[3]. This suggests a neuroprotective effect of astrocytes in PD. In this study, we further investigate the therapeutic potential of astroglia using optogenetics to stimulate astroglial cells in the substantia nigra (SNc) of rats injected with 6-OHDA. Briefly, rats were injected unilaterally with 6-OHDA into the dorsal striatum followed the next day by optogenetic stimulation of astroglia within the SNc. The rats were then tested on several behavioral tests either 8- or 21-days post 6-OHDA administration. While there was no significant effect of the lesion 8 days post 6-OHDA administration, there were, as expected, significant motor deficits 21 days post lesion. Interestingly, these deficits were attenuated with stimulation of SNc astroglia. In addition, a significant decrease in tyrosine hydroxylase (TH) positive neurons was noted in lesioned animals that was also attenuated with optogenetic stimulation of SNc astroglia. Taken together, this suggests an astroglial-induced neuroprotective effect at both the cellular and behavioral level. RNA-sequencing analysis of the SNc revealed differentially expressed genes that are implicated in microglial activation, immune pathways, and cytokine signaling. Altogether, results from this sequencing analysis further supports the notion that multi-cellular cross-talk is integral to neurodegeneration and neuroprotective processes.

**35. Stress and relapse: positive or negative reinforcement?**
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Introduction: Why does exposure to stressful stimuli precipitate drug-seeking and drug-taking? The negative reinforcement hypothesis posits that drugs of abuse are sought and consumed to alleviate the aversive state characteristic of most stressful responses. In contrast, the positive reinforcement hypothesis suggests that, because of similar neurobiology, stressors prime

incentive states characteristic of drug reinforcers. To test these opposing hypotheses, we investigated the affective and reinforcing properties of yohimbine; an antagonist of presynaptic alpha-2 adrenergic receptors which is well known to reinstate drug-seeking in rodents and drug cravings in humans. Methods: Using male and female Sprague-Dawley rats we assessed the effect of yohimbine (1.25 mg/kg, intraperitoneally) on blood serum corticosterone (CORT) levels, locomotor activity, place conditioning (1.25 mg/kg, 4 pairings, unbiased design), and intravenous self-administration (0.125, 0.25, 0.5 mg/kg/infusion). Results: As anticipated, systemic injections of a yohimbine dose known to precipitate alcohol, cocaine, and heroin seeking, elevated CORT levels. Surprisingly, the same dose induced psychomotor stimulation and a robust place preference in both male and female subjects. Yohimbine also supported reliable self-administration: both male and female rats acquired the lever-pressing response after only 6 short-access (1 hour) sessions on a fixed ratio. Moreover, in 3 h sessions, total yohimbine intake was modulated by dose per infusion, and was maintained even when drug-paired cues were removed. Conclusions: While yohimbine clearly acts as a pharmacological stressor in many respects (increased CORT in this study, and in other studies: increased plasma norepinephrine metabolites, blood pressure, and heart rate), it also possesses stimulatory, incentive, and reinforcing effects that are typical of psychostimulant drugs like cocaine or amphetamine, and which may be responsible for priming further drug seeking. These findings not only contribute to our understanding of the role of stress in relapse, but also open the possibility of potential clinical applications of this chemical reinforcer.

**36. A mesolimbic basis of infradian sleep-wake rhythms: relevance for bipolar disorder**

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Introduction: The circadian clock together with the daily light:dark cycle drives 24h sleep-wake rhythm. However, there also seem to exist a dopaminergic oscillator (DO) which can drive sleep-wake rhythms outside the circadian range. The DO associated rhythms can manifest when mice or rats are in a state of hyperdopaminergia, e.g., upon exposure to methamphetamine (Meth). Of note, the rest:activity patterns observed under chronic meth-treatment in mice exhibit profound resemblance to the aberrant sleep:wake patterns seen in cycling bipolar disorder (BD) subjects. This study aims to uncover the neural basis of the DO and to establish infradian rhythmic mice as model for bipolar cycling. Methods: For infradian rhythm induction, mice were chronically exposed to Meth per drinking water. Sleep/locomotor activity was recorded using passive infra-red sensors or running wheels. Mania-related behaviors were assessed by video-recording of locomotor activity in the open field arena. For neural substrate identification, dopamine (DA) neurons of the ventral tegmental area (VTA) were manipulated using genetic and pharmacological strategies. Results: Sleep length, hyperactivity, and mania-associated spatial movements fluctuated in synchrony with the 48h rest:activity rhythms that mice regularly develop upon chronic exposure to high concentrations of Meth via drinking water. Ablation of either VTA DA neurons or DA neuronal processes in the nucleus accumbens (NAc) led to a loss of bipolar-like, infradian sleep-wake pattern emergence, while circadian rhythmicity remained unaffected. Conclusions: 48h rhythmic mice recapitulate important aspects of 48h cycling in BD suggesting that they can serve as a model for cyclicity or mood-state switch in BD. Further, NAc-projecting DA neurons of the VTA are necessary for the generation of infradian, BD-like sleep-wake patterns, which is in line with a role as neuronal substrate for the DO and BD cycling.

### 37. Neural correlates of working memory in adults with addiction: a pilot exploratory analysis

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Introduction: Working memory (WM) impairment is a common feature in adults with substance use disorders that could interfere with addiction treatments. Aim: To functionally map brain regions involved in WM in a subsample of treatment-seeking participants in the Cognitive Dysfunction in the Addictions study at CAMH, and to investigate their relationships with substance use and depression.
Methods: Data was analyzed from forty-two adults (14 females, mean age 41.4±10.9 years, self-reported Primary Substance: Alcohol – N=32, Cannabis – N=9, Stimulants – N=1), who performed a verbal n-back WM task during an fMRI scan. Brain activations related to WM updating in 2-back vs 0-back conditions were assessed with one-sample t-tests in the entire cohort (FPR, $p<0.001$, cluster-threshold<0.001). Associations between WM, self-reported alcohol/substance use, and depression, assessed via the Alcohol and Drug Use Disorder Identification Tests (AUDIT and DUDIT), and the Patient Health Questionnaire (PHQ-9), respectively, were examined with linear regressions, while controlling for age, sex, and task performance (FPR, $p<0.05$, cluster threshold<0.001).
Results: Group analysis showed significant WM activations in prefrontal, dorsolateral, and precentral cortex areas, insula, and cerebellum, consistent with previous studies in addiction and healthy cohorts. Greater alcohol use positively correlated with activity in the left postcentral and right superior temporal cortex, whereas greater substance use was negatively correlated with left superior frontal cortex activity. Higher depressive symptoms were positively associated with medial superior frontal cortex activity, and negatively associated with right cerebellum activity.
Conclusion: This study suggests that among adults with addictions, those with greater alcohol use or depressive symptoms may require greater activation of frontotemporal regions to achieve or maintain certain WM performance. Greater use of substances other than alcohol was, conversely, associated with lower activation in non-overlapping left frontal regions. These associations could indicate compensatory mechanisms or poorly modulating brain activity, as a consequence of frontoparietal circuitry impairments in addiction.

### 38. Longitudinal investigation of metabolic changes, weight gain, and medication exposure in first episode psychosis

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Introduction: Poor cardiovascular health is the most frequent cause of death in schizophrenia, with obesity up to 3.5 times more likely. We evaluated medication exposure longitudinally in first episode psychosis (FEP) to delineate the interplay between medication, weight gain, and

metabolic markers.
Methods: Participants with FEP (173) were recruited during first hospitalization and evaluated again on average 39 days later. Healthy controls (204) were also assessed at that time. At each time we collected BMI and fasting venous blood samples. For participants with FEP, we collected cumulative and average daily antipsychotic exposure between visits, which we further categorized into metabolically problematic (clozapine, olanzapine, sertindole and quetiapine) or not. We tested for associations between medication exposure, BMI, and metabolites using linear modeling while controlling for age and sex. Longitudinal analyses additionally controlled for baseline BMI and the interval between visits.
Results: BMI significantly increased between time points. The increase was highest in those with lower baseline BMI, and was associated with exposure to metabolically problematic antipsychotics. Relative to controls, participants with FEP had significantly higher and more abnormal BMI, TGC, and prolactin, and lower fT4 and HDL. In participants with FEP, higher BMI was also associated with higher TGC and TSH, and lower HDL. Medication exposure was not associated with metabolic markers. Conclusion: Participants with FEP showed BMI increase in a short period that was associated with exposure to specific medications, and metabolic changes consistent with metabolic syndrome. Greater care should be taken when prescribing metabolically problematic antipsychotics for people with lower BMI.

### 39. Bipolar disorders and body mass index predict patterns of cortical and subcortical alterations – ENIGMA study in 2 443 individuals

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Introduction: Rates of obesity have reached epidemic proportions, especially among people with psychiatric disorders. While the effects of obesity on the brain are of major interest in medicine, they remain markedly under-researched in psychiatry.
Methods: We obtained body mass index (BMI) and MRI-derived regional cortical thickness, surface area, and subcortical volume in 838 individuals with bipolar disorders (BD) and 1605 healthy controls from 14 sites within the ENIGMA-BD Working Group. We identified regionally specific patterns of morphology for each measure principal component analysis (PCA), and studied clinical characteristics associated with these whole-brain patterns.
Results: The first principal component accounted for 43.6% of variance in brain imaging measures, and was associated with relevant clinical and anthropometric measures, including diagnosis of bipolar disorders, age, BMI, and treatment with lithium or antipsychotics. Specifically, lower thickness was found in those with bipolar disorders, higher BMI, and older age. Lithium treatment was associated with preserved thickness, surface area and volume, while antipsychotic treatment was associated with lower thickness. These links with clinical correlates were strongest in superior temporal and frontal regions. Conclusion: We demonstrate new evidence that bipolar disorders and obesity are both uniquely and additively linked to widespread patterns of cortical and subcortical changes, which were weakest in those prescribed lithium and strongest in those prescribed antipsychotics. These findings motivate further research into the causality of these associations.

**40. Autonomic reactivity to emotional stimuli in a transdiagnostic sample of psychiatric patients**

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Alina Marin. Author, MD, PHD. Department of Psychiatry, Queen's University, Kingston, ON, Canada

Introduction: The relation between autonomic reactivity (AR) and emotion dysregulation (ED) has rarely been addressed across multiple psychiatric diagnoses. This pilot study aims to explore how non-invasive measures of autonomic reactivity: skin conductance response (SCR) and heart-rate reactivity (HRR) correlate with the behavioral assessment of ED in adult patients with attention deficit hyperactivity disorder (ADHD), borderline personality disorder (BPD), and bipolar spectrum disorders (BD).
Methods: Forty adult patients with diagnoses of BPD, BD, and/or ADHD viewed emotionally evocative images taken from the International Affective Picture System (IAPS) while physiological (SCR and HRR) and subjective reactions were recorded. Levels of ED were quantified via scores on the Difficulties in Emotion Regulation Scale (DERS-18). Comparisons of physiological and subjective reactions across the three types of stimuli were assessed with Friedman's test and the Wilcoxon multiple comparisons method as a post-hoc test.
Results: Mean valence ratings significantly differed among the three types of emotional stimuli (neutral, pleasant, unpleasant) for all participants. Pleasant image arousal ratings were significantly higher than neutral ratings, whereas unpleasant image arousal ratings were significantly lower than neutral images. Heart rate reactivity (HRR) was similar across valence conditions. Higher DERS-18 scores were associated with lower mean heart-rate reactivity (HRR), particularly for unpleasant images. Individuals with greater difficulty with emotional clarity and emotional acceptance showed lower HRR to pleasant or unpleasant stimuli. SCR amplitudes across emotional stimuli were not found to display any significant associations with clinical assessment scores but varied with the diagnosis. Conclusion: Our observed patterns of HRR and SCR amplitudes suggest that individuals with high levels of ED may exhibit a form of hypoarousal, indicating reduced sensory processing of emotional stimuli. Examining objective markers of autonomic reactivity (HR and SCR) in relation to subjective perceptions may provide a valuable index to characterize the dimension of emotion dysregulation.

**41. Using card games as knowledge translation tools: a pilot study based on the 2018 CANMAT and ISBD guidelines for the management of patients with bipolar disorder**

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Introduction: Knowledge translation initiatives are needed to reduce the gap between evidence-based recommendations and everyday practice. Interactive learning activities may facilitate engagement and understanding, longer retention of the information and higher satisfaction with the learning experience. The aim of this study was to develop and test the use of card games to teach and/or review the content of the 2018 CANMAT/ISBD guidelines for the treatment of bipolar disorder.
Methods: We created 3 card games based on guideline recommendations: a) TOP CHOICES: a 30-card game inspired by Top Trumps©. Each card lists one treatment option (medications, psychotherapies, ECT) and the objective is to learn about indications, evidence levels, safety and

tolerability profiles. Lithium is the Top Trump, the most valuable card; b) MONO: a 72-card game inspired by UNO© aimed to learn about available monotherapies. Medications are grouped in different colors according to their indications (mania, depression, maintenance) and one may use wildcards that represent medications with more than one indication (e.g., lithium, quetiapine); c) FIRST CHOICES: a 108-card game inspired by Monopoly Deal© designed to present first-line options for mania, bipolar depression, and maintenance treatments. Players collect different options of same-color sets (representing different treatment indications) and use action and "money" cards to make transactions and obtain more cards.
Results: A pilot session was held at the ISBD Conference in June 2023. Out of 30 participants, 12 provided feedback via an anonymous survey. All responders enjoyed playing the games and most (8/12) reported they were easy to play. All responders reported the games were helpful in reviewing the recommendations and most (11/12) reported they increased their motivation to learn more about the guidelines.
Conclusions: Card-games may be a fun and useful method to learn and/or review treatment recommendations and may be used as both a teaching and an implementation tool.

### 42. Rat ultrasonic vocalizations during the anticipation and experience of social interaction

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Introduction: Rats emit 50-kHz ultrasonic vocalizations (USVs) under different rewarding contexts, including during the anticipation and access to a playmate. However, the specific 50-kHz call subtypes recruited in these play-related behavioral states have not been directly compared. Here we investigated whether certain USV measures (i.e., call rate, call subtype prevalence) were differentially expressed during the anticipation versus the experience of social interaction. Additionally, we examined whether a beta blocker would inhibit the play-associated changes in USV measures, as previously shown with another rewarding stimulus (amphetamine administration).
Methods: Cagemate pairs of male Long-Evans rats were randomly allocated to Play and No-Play groups (n=8 pairs). Phase 1 consisted of behavioral testing for 8 consecutive days, whereas in Phase 2, the same daily behavioral testing was preceded by drug treatment, with either propranolol or saline. During behavioral testing, rats from the Play group were separated from their cage mate for 5 mins (i.e., 'pre-play' period) and then reunited for 5 mins (i.e., 'play' period). The control (i.e., No-Play) group was underwent the same procedure, except there was no reunion during the play period.
Results: In both Phases and test periods (pre-play and play), the Play group called at a higher rate than the No-Play group. As expected, during the play period the Play group tended to emit a greater number of trill calls and fewer flat calls than the No-Play group. Variations in other call subtypes were revealed during the pre-play period, a greater proportion of flat-trill calls and a lower proportion of short calls were emitted by the Play group in comparison the No-Play group. Propranolol had no detectable effect. Conclusion: The relative prevalence of trill and flat 50-kHz ultrasonic calls may reflect positive affect, consistent with previous findings, whereas reward anticipation appears to recruit other call subtypes. Funding: NSERC and CIHR.

### 43. Neuronal characterization of the prodromal stage in Parkinson's disease using a new a-synuclein-based mouse model

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Background: Depression is a common non-motor symptom that often emerges early, during the prodromal phase, of Parkinson's disease (PD). Emerging evidence has associated such depressive pathology with the distribution of a-synuclein (a-syn; PD-neuropathological hallmark) in the brainstem and limbic regions. Depression in PD is also linked to deficits in serotonergic (5-HT) functions before any clear degeneration of the dopamine (DA) system is evident.
Methods: Accordingly, we developed a new a-syn based model of PD to examine the progression of non-motor and motor deficits associated with 5-HT and DA impairments. We performed unilateral intracerebroventricular infusion of wild-type and A53T mutant a-syn preformed fibrils (PFF) in adult male C57/BL6 mice to evaluate the brain-wide direction of pathological a-syn spread and aggregation. To assess the behavioural changes forced swim, sucrose preference and open field tests were performed after ½, 1, 2, 3, 4 and 8 months post-surgery.
Results: We found that the PFFs (particularly the A53T mutant form) primarily induced signs of anxiety and depressive-like behaviors at multiple times starting 4 weeks up to 8 months post-surgery, whereas minimal motoric changes were secondarily observed after 4 months post-surgery. Digigate analyses revealed significant gait difficulties starting at the 4-month time. Initial p-a-syn immunostaining showed signs of accumulation within the dorsal raphe 5-HT cells, basolateral amygdala, hippocampal regions, nucleus accumbens and cortex as early as 1- and 4-months post-surgery. Ultra-resolution imaging approaches will be used to further characterize the nature of the a-syn aggregates. Conclusion: These preliminary results support the contention that a-syn might act as a common stimulus for mood by targeting 5HT cells preceded by motor pathology in PD.

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| Nexha, Adile | 2 | 2 |
| Noon, Ava Rae | 1 | 34 |
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| Pangborn, Nikki | 2 | 4 |
| Pappis, Lauren | 1 | 32 |
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| Peart, Davin | 1 | 27 |
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| Rahbarnia, Arya | 2 | 14 |
| Ramljak, Maja | 2 | 32 |
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| Richard, Jennifer | 2 | 9 |
| Richards, Janielle | 1 | 12 |
| Richer, Samuel | 1 | 1 |
| Rodrigue, Brandon | 2 | 16 |
| Sarwary, Meihan | 1 | 23 |
| Shao, Suyi | 1 | 8 |
| Sikic, Anita | 2 | 30 |
| Singh, Raghunath | 1 | 25 |
| Sodhi, Rupinder Kaur | 1 | 41 |
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| Vahid-Ansari, Faranak | 1 | 14 |
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