Canadian College of Neuropsychopharmacology
COLLÈGE CANADIEN DE NEUROPSYCHOPHARMACOLOGIE

CCNP – 48th Annual Meeting

Program Overview



Faculty Club, University of Toronto

September 23 – 25, 2026

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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.

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YOUR LOCAL ORGANIZING COMMITTEE (LOC)

Chair: Daniel Mueller (University of Toronto)

CCNP's Executive

CCNP's Councillors

Dr. Jerome Foo (University of Alberta)

Ms. Maia Zilberman (University of Toronto)

A sincere thank you to our LOC for their hard work, dedication and patience in the organization of this year's Annual Meeting



Our sincere thanks to The Faculty Club, the Division of Teaching Laboratories and the Campus Moving Team, University of Toronto!



Build Your Peer Review Skills with JPN's Early Career Reviewer Program

The *Journal of Psychiatry and Neuroscience* (JPN) Early Career Reviewer Program is a pilot initiative designed to equip emerging researchers with the knowledge, skills, and mentorship needed to participate confidently in the peer review process.

Created in collaboration with the Canadian College of Neuropsychopharmacology (CCNP), the program supports professional development while helping build a diverse and qualified community of future reviewers in psychiatry, neuroscience, and related disciplines.

Who can apply?

Applicants must be current CCNP members and be enrolled or appointed as a PhD Student, MD Student, Clinical Fellow, or Postdoctoral Fellow. A CV is required as part of the application. PhD and MD students must also provide a supporting statement from their supervisor.

Applications are open until January 31, 2027.

Learn more about the program and apply.

MEET OUR KEYNOTE SPEAKERS

Dr. Martin Paulus
Scientific Director and President
Laureate Institute for Brain Research



Dr. Martin P. Paulus has built a distinguished career at the forefront of psychiatric neuroscience, dedicated to understanding the complex brain mechanisms underlying mental illness. Currently serving as the Scientific Director and President of the Laureate Institute for Brain Research (LIBR) in Tulsa, Oklahoma, he leads a comprehensive research program aimed at translating neurobiological discoveries into tangible clinical tools. His work is characterized by an integrative approach that combines computational modeling, multimodal neuroimaging, and interoceptive science to better understand and treat conditions like anxiety, depression, and substance use disorders.

The title of his keynote presentation is: **"Semaglutide and Psychiatric Service Use in Major Depressive Disorder: A Target Trial Emulation in All of Us"**

Dr. Ana Andreazza
Professor, Departments of Pharmacology & Toxicology and Psychiatry, University of Toronto
Tier II Canada Research Chair in Molecular Pharmacology of Mood Disorders
Thomas C. Zachos Chair in Mitochondrial Research



Dr. Ana Andreazza's research focuses on mitochondrial bioenergetics across mood disorders, organ transplantation, and regenerative medicine. She has identified mitochondrial gene dysfunctions in bipolar disorder and pioneered the use of human brain organoids to study bioenergetic mechanisms underlying psychiatric illness and treatment response. Recently awarded $24M through the NFRF Transformation program, her collaborative translational research aims to advance precision therapeutics and improve clinical outcomes in mental health and beyond.

The title of her keynote presentation is**: "Mitochondrial Bioenergetics in Mood Disorders: From Organoids to Clinical Impact"**

OUR MAJOR AWARDS WINNERS

Dr. Benjamin Goldstein

CCNP Medal



Dr. Benjamin Goldstein is a Professor and Vice Chair of Psychiatry, cross-appointed in Pharmacology, at the University of Toronto. He holds the RBC Investments Chair at CAMH, where he is Scientific Director of the Centre for Youth Bipolar Disorder. Dr. Goldstein's efforts focus on bipolar disorder in youth. His team seeks to generate insights regarding the association of vascular health with bipolar disorder and brain health in youth, with the goal of informing preventive efforts focusing simultaneously on physical and mental health. Dr. Goldstein has authored over 350 scientific articles, and has received national and international awards for his research.

Dr. Jerry Warsh

Heinz Lehmann Award - For Outstanding Contributions to Neuropsychopharmacology



Dr. Warsh is currently an Emeritus Senior Scientist at the Campbell Family Mental Health Research Institute and Staff Psychiatrist in the Mood Disorders Clinic CAMH, and Professor, Department of Psychiatry and Emeritus Professor, Institute of Medical Sciences, at the University of Toronto. He was a founding and lifelong member of the CCNP. He has maintained an active career in biological psychiatry and neuropharmacology research on mood disorders since 1974. His research contributions have primarily focused on the molecular pathophysiology of bipolar disorder, spanning the development of quantitative methods for neurotransmitters and psychotropic drugs for translational studies to molecular, cellular, and genetic studies of intracellular signal transduction and calcium dynamics in bipolar disorder. As a former Director of Research at the Clarke Institute of Psychiatry, he contributed to the development and implementation of the Positron Emission Tomography facility and the establishment of the Neurogenetics Laboratory and the recruitment of its director, Dr. James Kennedy. He has held funding throughout his career from the MRC, Ontario Mental Health Foundation, and the Stanley Research Foundation. He has been the recipient of the Paul Christie and John Dewan awards from the Ontario Mental Health Foundation and a Distinguished Investigator Award from NARSAD for his research on mood disorders. He is currently conducting active research on mood and comorbid disorders through various collaborations in the Brain Health Imaging Centre at CAMH and has embarked with colleagues on neuroimaging and molecular studies of the role of blood-brain barrier disruption in the pathophysiology of bipolar disorders.

Dr. Lena Palaniyappan

Innovations in Neuropsychopharmacology Research – For Outstanding Innovations in Neuropsychopharmacology by an Individual or Group



Dr. Lena Palaniyappan is an early intervention psychiatrist with training in neuroimaging and systems neuroscience. His main research interest over the past two decades has been finding effective means of prevention and early intervention for youth-onset mental illness, particularly psychotic and affective disorders. His discoveries include: 1) identifying dysfunction of salience-processing brain regions as a core mechanism in psychosis, now among the more consistently replicated circuit-level findings in the field; 2) pioneering the application of ultra-high-field MRI (7T) in untreated psychosis to study glutamate and antioxidant neurochemistry; and 3) innovative studies of thought disorder using natural language processing approaches, and establishing a TalkBank for Psychosis. He is ranked as one of the most productive authors globally in schizophrenia research over the past 5 years. As Director of the Centre of Excellence in Youth Mental Health at the Douglas Research Centre, McGill University, he leads a research programme funded by CIHR, FRQS, the Wellcome Trust (UK), and several philanthropists. He serves as Editor-in-Chief (Clinical) of the Journal of Psychiatry and Neuroscience. He has trained >40 graduate and postgraduate researchers, several of whom now hold independent faculty positions and prestigious research awards in their own right.

Dr. Corina Nagy

Early Career Investigator Award – For Outstanding Contributions to Neuropsychopharmacology by an Early Career Investigator



Dr. Corina Nagy is an Associate Professor in the Department of Psychiatry at McGill University and a principal investigator at the Douglas Research Centre. Her research examines the molecular and cellular features of the human brain associated with vulnerability to major depressive disorder, with particular emphasis on sex-differences. By integrating single-cell multiomics, and spatial approaches with human postmortem studies and animal models, her laboratory investigates how these patterns vary across cell types, brain regions, and over time using pseudo longitudinal modeling.

Dr. Leah Mayo

Early Career Investigator Award – For Outstanding Contributions to Neuropsychopharmacology by an Early Career Investigator



Leah Mayo is the Parker Psychedelics Research Chair and an Associate Professor in the Department of Psychiatry, as well as a member of the Hotchkiss Brain Institute and the Mathison Centre for Mental Health Research & Education at the University of Calgary. Her research focuses on developing novel pharmacotherapeutic interventions for stress-related mental health disorders, such as substance use disorders and post-traumatic stress disorder, with a particular focus on cannabinoid- and psychedelic-based therapeutic opportunities. The work of her research team – the Psychedelic and Cannabinoid Therapeutics (PaCT) Lab – spans the translational spectrum, encompassing animal models, experimental studies in healthy humans, mechanism-informed clinical trials, and community-partnered research, using an iterative approach that allows for communication between all levels of translation. The ultimate goal is to produce novel interventions that are not only grounded in solid scientific data, but are also aligned with the needs of the communities that will be using them.

SYMPOSIA SESSIONS

Thursday, September 24

Symposium 1

Chair: Dr. Joshua Rosenblat (University Health Network, University of Toronto)

Symposium Title: "Ketamine for Depression: From Bench to Bedside and Back"

Synopsis: Over the past 25 years, ketamine has emerged as a promising treatment for depression and related psychiatric conditions. Ketamine is a dissociative anesthetic that has been found to have rapid and robust antidepressant effects. This session will present new research findings from clinical efficacy trials, biomarker and neurobiologically focused clinical studies and pre-clinical work providing a broad, translational perspective on ketamine research, from bench to bedside and back. Dr. Johnston will start the session with exploring the impact of ketamine metabolites on cerebral organoids. Dr. Price will then present a series of clinical studies exploring markers of neuroplasticity with ketamine. Dr. Hu will discuss data from a clinical trial showing that ketamine improves social anhedonia in depression, along with late breaking biomarker analyses. Lastly, Ms. Orsini will present the world's first RCT evaluating serial ketamine infusions for bipolar depression, demonstrating efficacy and safety in this practice changing clinical trial. This session will include speakers from three different institutions, including three international speakers. All four speakers are women, and the chair is a male person of colour. Exemplifying the depth and breadth of CCNP, our group is from all career stages (graduate student [Orsini], post-doctoral researchers [Johnston and Hu], associate professor [Rosenblat] and full professor [Price]), diverse training backgrounds (psychiatry, psychology and non-clinical) and includes basic scientists, neurobiologists and clinical researchers.

Speaker 1: Dr. Jenessa Johnston, National Institute of Mental Health (NIMH/NIH), USA

Title: *"Cerebral organoids from healthy volunteers and treatment-resistant depression patients reveal diagnostic-specific responses to (2R,6R)-hydroxynorketamine"*

Summary: Induced pluripotent stem cell (iPSC)-derived cerebral organoids provide a novel platform to investigate brain-specific molecular changes relevant to treatment-resistant depression (TRD). Cell lines from 5 healthy volunteers (HVs) and 5 TRD participants in an ongoing NIMH clinical trial were used to generate mature cerebral organoids, which were subsequently treated with (2R,6R)-HNK, a major ketamine metabolite. TRD organoids significantly overlapped with known depressive disorder gene-sets, confirming a disease-relevant phenotype. TRD and HVs had disparate responses to HNK, suggesting diagnostic-specific responsiveness to therapeutics and further validity of iPSC-derived therapeutics as a novel methodological approach to depression.

Speaker 2: Professor Rebecca Price, University of Pittsburgh, USA

Title: *"Specifying and leveraging rapid effects of ketamine on plasticity mechanisms across levels of analysis: Findings from clinical trials"*

Summary: Ketamine is known for its rapid antidepressant effect, which is hypothesized to be rooted in rapid enhancement of neuroplasticity mechanisms. Using data from several clinical trials, this talk will cover ketamine's impact across a range of putative 'plasticity' markers in human patients. Specific examples will be provided for how these mechanistic insights have been leveraged to optimize treatment outcomes.

Speaker 3: Dr. Hiroe Imai Hu, National Institute of Mental Health (NIH/NIMH), Experimental Therapeutics and Pathophysiology Branch, USA

Title: *"Exploring the entactogenic effects of ketamine"*

Summary: Ketamine has recently been associated with entactogenic effects, promoting prosocial behavior and hedonic pleasures associated with social interactions. This session will discuss data from a clinical trial on patients with treatment resistant depression and suicidal thoughts and behavior that ketamine improves social anhedonia and its relationship to general antidepressant effects and dissociative symptoms. Late breaking data on pre and post-ketamine levels of circulating plasma oxytocin will also be presented. Experimental design and outcome measurements to optimize the investigation of entactogenic effects of rapid acting antidepressant will be proposed and probed to open discussions.

Speaker 4: Diana Orsini, Department of Pharmacology & Toxicology, University of Toronto

Title: *"Serial Ketamine Infusions for Treatment-Resistant Bipolar Depression (NCT05004896)"*

Summary: Previous randomized controlled trials (RCTs) have supported the acute antidepressant efficacy and safety of IV ketamine for treatment resistant depression (TRD) in major depressive disorder; however, no RCTs have evaluated the effects of an acute course of IV ketamine for TRD in bipolar disorder (BD) specifically (TRBD). We conducted a multi-site, double-blinded, midazolam-controlled RCT to evaluate safety and efficacy of an acute course of IV ketamine for moderate to severe TRBD. Mean MADRS change from baseline to day 14 was significantly greater with ketamine versus midazolam (between group difference = -7.3 points; 95% CI: -12.0 to -2.5; p = 0.003; n=68) in keeping with a large antidepressant effect size. No cases of mania, psychosis or suicide attempts were observed.

Symposium 2

Chair: Robert McCullumsmith (University of Toledo)

Symposium Title: "Can brain metabolism be leveraged to treat severe mental illness?"

Synopsis: Recent work implicates abnormalities of metabolic pathways and processes in severe mental illness (SMI). Metabolic systems implicated in SMI include mitochondrial function, glucose utilization, insulin signaling, and many others, with evidence suggesting changes in these

systems influenced by genetic, epigenetic, and environmental factors. In this panel, we present new unpublished work that explores metabolic disruptions in severe mental illness, focusing on assessment of metabolic function as well as interventions that may improve mental health outcomes via metabolic interventions.

Speaker 1: Dr. Mahavir Agarwal, Schizophrenia Division, Centre for Addiction and Mental Health, Department of Psychiatry, University of Toronto, Toronto, ON

Title: *"Efficacy Data from a Psychiatrist-Led Clinic for Metabolic Health in Severe Mental Illness: A Retrospective Chart Review Study"*

Summary: Dr. Agarwal will present data from a large naturalistic retrospective cohort evaluating the impact of a psychiatrist-led, integrated model of care that combines non-pharmacological and pharmacological interventions to manage metabolic dysfunction in individuals with SMI. The results show that 37.5% patients lost ≥5% of their baseline body weight during the 12-month study period suggesting that psychiatrist-led care for metabolic dysfunction in mental illness is effective in reducing psychotropic-induced weight gain.

Speaker 2: Dr. Laura Rowland, Maryland Psychiatric Research Center Department of Psychiatry University of Maryland School of Medicine

Title: *"3T MRS-based glucose and lactate levels in living patients with schizophrenia"*

Summary: Dr. Rowland will present data from a project that examined brain and peripheral metabolic measures in people with schizophrenia and healthy controls. Glucose and lactate levels measured with proton magnetic resonance spectroscopy (MRS), cognition and psychiatric symptoms, and blood measures of insulin resistance will be discussed.

Speaker 3: Dr. Margaret Hahn, Schizophrenia Division, Centre for Addiction and Mental Health, Toronto, ON, Canada Department of Psychiatry, University of Toronto, Toronto, ON

Title: *"Topiramate in clozapine-treated patients with schizophrenia spectrum disorders: Effects on weight and psychopathology"*

Summary: Dr. Hahn will present data from a randomized control trial (RCT) demonstrating that topiramate significantly lowers body weight, and as an secondary outcome, improves psychopathology compared to placebo in treatment refractory, overweight or obese patients with schizophrenia receiving clozapine.

Speaker 4: Dr. Robert McCullumsmith, Department of Neurosciences and Psychiatry, University of Toledo College of Medicine

Title: *"Alterations of canonical insulin signaling pathways in the brain in schizophrenia"*

Summary: Dr. McCullumsmith will present data from postmortem DLPFC brain samples from subjects with schizophrenia and a control group that support the hypothesis that

canonical insulin signaling pathway function is disrupted in this illness. Findings include alterations in SGK1 and AKT1 kinase expression and activity. These kinases regulate structural plasticity of synapses, as well as immune responses in the brain, connecting these data to the prevailing hypotheses of schizophrenia as a disorder of synaptic turnover.

Symposium 3

Chair: Caleb Browne (Brain Health Imaging Centre, Centre for Addiction and Mental Health; Departments of Psychiatry and Physiology, University of Toronto

Symposium Title: "Multi-Scale Signatures of Addiction: From Genetic Risk to Circuit Mechanisms"

Synopsis: Substance use disorders represent a major public health challenge, with high rates of relapse and limited effective treatment options. Addressing this requires a deeper understanding of addiction that emerges from integrating insights across multiple domains of neuroscience and levels of analysis. This symposium brings together a diverse group of investigators from multiple Canadian institutions, integrating complementary clinical and preclinical approaches to examine neurobiological factors that shape brain function and behavior in addiction. Isabelle Boileau (Centre for Addiction and Mental Health) will outline human positron emission tomography studies of cannabis and alcohol use disorders, demonstrating that the endocannabinoid enzyme FAAH is altered during early abstinence and linked to withdrawal-related phenotypes and relapse risk. Jibran Khokhar (University of Western Ontario) will examine the genetic basis of cannabis use through CADM2, using a knockout model to reveal altered cannabinoid sensitivity and mesocortical dopamine dynamics. Leah Mayo (University of Calgary) will investigate how acute and chronic stimulant and opioid exposure shape stress reactivity, mood, and endocannabinoid function across timescales using pharmacological and biomarker approaches. Caleb Browne (Centre for Addiction and Mental Health) will define circuit-level mechanisms of relapse using a rodent model of opioid self-administration, showing that ventral hippocampal activity is stabilized through epigenetic remodeling to support persistent drug-seeking throughout abstinence. Together, this session highlights how complementary lines of research converge on key factors that promote addiction, spanning levels of analysis from brain systems to molecular mechanisms, and informing the development of novel therapeutic strategies.

Speaker 1: Dr. Isabelle Boileau, Brain Health Imaging Centre, Centre for Addiction and Mental Health; Department of Psychiatry, University of Toronto

Title: *"Relapse in Cannabis and Alcohol Use Disorders: A Focus on FAAH and Early Abstinence"*

Summary: Relapse during early abstinence remains a major clinical challenge in both cannabis and alcohol use disorders (CUD and AUD). Preclinical and human evidence suggests that the endocannabinoid system, and in particular the enzyme fatty acid amide hydrolase (FAAH), may play a critical role in relapse vulnerability. In this study,

we used positron emission tomography (PET) with the FAAH radiotracer [11C]CURB to investigate changes in FAAH levels during short-term abstinence. Participants included individuals with CUD and individuals with AUD, who underwent PET scanning before and after a brief period of abstinence. FAAH binding was linked to behavioral and clinical measures associated with withdrawal severity and relapse risk. Preliminary results indicate that FAAH availability maybe altered in abstinence and is associated with withdrawal-related phenotypes. These findings support targeting FAAH as a biomarker for relapse vulnerability and as a candidate for early intervention strategies.

Speaker 2: Dr. Jibran Khokhar, Anatomy and Cell Biology, Schulich School of Medicine and Dentistry, Western University

Title: *"Finding a Needle in the Cannabis Use GWAS: A Role for CADM2?"*

Summary: Cell adhesion molecule 2 (CADM2) has been implicated in cannabis use phenotypes in human genetic studies, yet the biological basis of this association remains unclear. Using a Cadm2 knockout model in rodents, we find reduced preference for cannabis edibles, altered sensitivity to THC across tetrad and prepulse inhibition assays, and earlier, prolonged mesocortical dopamine transients during cannabis vapor exposure. These effects occur without genotype differences in brain or blood levels of THC or its primary metabolite, 11-OH-THC, suggesting a central circuit mechanism underlying CADM2-associated differences in cannabis-related behavior.

Speaker 3: Dr. Leah Mayo, Mathison Centre for Mental Health Research and Education, Hotchkiss Brain Institute; Department of Psychiatry, University of Calgary

Title: *"Effects of Acute and Chronic Stimulant and Opioid Administration on Stress Reactivity and Endocannabinoid Function in Humans"*

Summary: Stress and drug use are intricately intertwined – stress can precipitate substance use, while both acute and chronic use alter stress reactivity. The endocannabinoid (eCB) system is a key mediator of stress reactivity, and its diverse pharmacology enables multiple modes of targeting beyond direct receptor binding. Thus, understanding how acute and chronic drug exposure impacts eCB function and related behaviors may highlight novel pharmacotherapeutic opportunities. Across a series of human studies, we examine how acute and chronic stimulant and opioid use impact stress, mood, and eCB function. Using pharmacological probes, blood-based biomarkers, and laboratory stress paradigms, we identify both short- and long-term disruptions in eCB signaling. Together, these studies highlight short- and long-term effects of substance use on stress and eCB function, pointing to novel therapeutic opportunities for substance use disorders.

Speaker 4: Dr. Caleb Browne, Brain Health Imaging Centre, Centre for Addiction and Mental Health; Departments of Psychiatry and Physiology, University of Toronto

Title: *"Functional and Molecular Adaptations in the Ventral Hippocampus Supporting Relapse Vulnerability"*

Summary: Relapse in opioid use disorder is mediated by neuroadaptations that prime motivational circuits for drug-seeking. The ventral hippocampus (vHPC), which links memory processes with motivation, is well positioned to drive relapse. Using a mouse

intravenous heroin self-administration model, we combine fiber photometry with transcriptional and epigenetic profiling to define vHPC adaptations that persist through abstinence. vHPC neurons are strongly engaged during drug intake and reactivated during drug-seeking after protracted abstinence, a role in encoding and reactivation of drug-associated representations that support drug-seeking. Molecular profiling reveals coordinated regulation of epigenetically controlled gene networks, including Kmt2a-associated H3K4me1 modifications at glutamatergic loci, suggesting stabilization of these circuits. Together, these findings support a model in which drug-evoked vHPC activity is epigenetically consolidated to promote relapse vulnerability.

Symposium 4

Chairs: Lena Quilty & Yuliya Nikolova (Centre for Addiction and Mental Health; University of Toronto)

Symposium Title: "Multi-Scale Signatures of Addiction: From Genetic Risk to Circuit Mechanisms"

Synopsis: Substance use disorders (SUDs), including Alcohol Use Disorder (AUD), are major public health concerns. Cognitive impairments—particularly in executive functioning (EF)—are central to addiction models, yet gaps remain in understanding how EF relates to neural circuits, biomarkers, disorder heterogeneity, and functional outcomes. Addressing these gaps requires integrated clinical, biomedical, and preclinical research, and large naturalistic samples reflecting the complexity of real-world SUD populations. In response to this challenge, the Cognitive Dysfunction in the Addictions (CDiA) Program was launched in 2021 as an interdisciplinary initiative examining how EF shapes functional outcomes in SUDs. CDiA collects clinical, cognitive, neuroimaging and peripheral biomarker data from adults seeking treatment for diverse SUDs (N=400), and serves as a platform for observational studies and clinical trials. An integrated preclinical component evaluates analogous cognitive constructs in rodent models to support bidirectional translation. In this Symposium, we present early CDiA findings spanning multiple levels of investigation. First, we identify novel associations between substantia nigra integrity and cognitive performance across SUDs. Second, we show that circulating inflammatory biomarkers track with distinct clinical and cognitive profiles, demonstrating that peripheral immune signatures capture meaningful heterogeneity in SUDs. Extending these findings, a rodent model of chronic alcohol use shows that withdrawal produces distinct inflammatory signatures differentiating animals with and without heightened impulsivity. Lastly, we present a proof-of-concept clinical trial, evaluating feasibility and tolerability of a 4-week neuromodulation intervention to the frontal cortex with repetitive transcranial magnetic stimulation in Cannabis Use Disorder (CUD). Collectively, these findings highlight novel, translationally relevant biomarkers and therapeutic targets for SUDs.

Speaker 1: Dr. Yuliya Nikolova, Centre for Addiction and Mental Health; University of Toronto

Title: *"Substantia Nigra Integrity as a Biomarker of Cognition in Substance Use Disorders"*

Summary: Substance use disorders (SUDs) are associated with structural alterations in key dopaminergic nuclei, including the Substantia Nigra (SN). Despite the SN's known modulatory role in cognitively relevant brain circuits, the cognitive implications of these

alterations remain uncharacterized. Here, we investigated how SN integrity maps onto cognitive performance in adults with diverse SUDs. CDiA participants (n=107, age: 39+/-11 years) underwent neuromelanin-sensitive magnetic resonance imaging to assess SN structure, indexed via contrast-to-noise ratios (CNR). Voxel-wise linear regressions evaluated the link between CNR and cognition, measured via the Central Nervous System–Vital Signs Neurocognition Index (NCI) and its subdomain scores. Higher CNR in the SN was associated with worse NCI (p=0.0168, corrected), driven primarily by the EF-related Complex Attention domain score (p=0.0190, corrected). These results highlight SN integrity as a novel biomarker of cognitive dysfunction in SUDs.

Speaker 2: Dr. Erica Vieira, Centre for Addiction and Mental Health; University of Toronto

Title: *"Inflammation, Cognition, and Substance Use: A Multimodal Biomarker Framework for Substance Use Disorders"*

Summary: Circulating inflammatory biomarkers robustly track with distinct clinical and cognitive profiles, providing evidence that peripheral immune signatures capture meaningful heterogeneity in neuropsychiatric disorders. However, the integrated analysis of these domains within real-world cohorts of individuals with substance use disorders (SUDs) remains underexplored. In this presentation, we examine the multimodal integration of biomarker, cognitive, and clinical measures to identify biologically informed subgroups characterized by differential executive dysfunction and functional impairment. Preliminary findings from the CDiA cohort support a mechanistic link between peripheral immune signaling and neurocognitive processes relevant to SUDs. Collectively, this work establishes circulating inflammatory markers as scalable, biologically grounded tools to support precision-oriented approaches in SUDs.

Speaker 3: Dr. Thomas Prevot, Centre for Addiction and Mental Health; University of Toronto

Title: *"Alcohol Withdrawal Reveals Inflammatory Correlates of Impulsivity in Rats"*

Summary: This study investigates alcohol withdrawal effects in a rat model of AUD, focusing on inflammatory markers and impulsivity using the 5-choice serial reaction time task, a validated measure of EF-like function in rodents. Male rats (n=24) were trained to respond to a light stimulus in one of five apertures with a short inter-trial interval, achieving >80% accuracy and <20% omissions. Following training, rats received 4 cycles (1 cycle=5 days ethanol + 2 days withdrawal) ethanol (7.5% w/v) in a Boost diet and blood samples were analyzed for peripheral inflammatory markers. Half of the rats displayed increased impulsivity (responders) compared to controls, while the other half showed no impulsivity (non-responders). Pro- and anti-inflammatory cytokine profiles differed between responders and non-responders. These findings suggest peripheral inflammatory profiles may predict impulsivity during alcohol withdrawal, which may have important translational implications for AUD treatment.

Speaker 4: Dr. Victor Tang, Centre for Addiction and Mental Health; University of Toronto

Title: *"Development of a Novel, Scalable, Neurobiologically-Guided Transcranial Magnetic Stimulation Protocol for the Treatment of Cannabis Use Disorder"*

Summary: Repetitive transcranial magnetic stimulation (rTMS) is a promising brain-based approach in addiction treatment. Neurobiological models link drug craving to EF deficits in the prefrontal cortex (PFC), which plays a key role in cue processing and inhibiting drug-seeking behaviour. Thus, enhancing deficient PFC activity in CUD may increase top-down EF regulation of a dysfunctional reward system. Deeper regions such as the insula also contribute to the addictive process by mediating interoception and integration of emotional states. We present a proof-of-concept pilot clinical trial, leveraging CDiA infrastructure, that shows feasibility and tolerability of a 4-week course of rTMS to the bilateral PFC and insula as a treatment for CUD. Preliminary findings of potential pre/post rTMS changes in reducing cannabis use, improving EF, and correlations with PFC/insula connectivity will be discussed. This work may support a novel, scalable, and cost-effective brain-based intervention for CUD.

Symposium 5

Chair: Dr. Venkat Bhat (University of Toronto; Unity Health Toronto, University Health Network)

Symposium Title: "Artificial Intelligence in Psychiatry: From Prediction and Data Platforms to Generative and Agentic Systems"

Chair Affiliations: University of Toronto; Unity Health Toronto, University Health

Synopsis: Artificial intelligence (AI) is rapidly transforming psychiatry across clinical care, neuroscience, and health systems. Contemporary advances span predictive modeling, large-scale data platforms, generative AI, and multimodal approaches capable of integrating behavioral, linguistic, and biological data. Together, these developments are reshaping how mental disorders are understood, assessed, and treated, while raising critical questions regarding implementation, safety, interpretability, and clinical utility. This symposium will provide a timely, interdisciplinary, and multi-institutional perspective across these domains.

Dr. Bhat will introduce clinical applications of generative AI in psychiatry, including conversational agents and multimodal decision support tools that enable measurement-based and personalized care, while highlighting challenges related to safety, regulation, and workflow integration. Dr. Glatard will present advances in scalable, reproducible, and privacy-preserving data platforms, emphasizing federated approaches that support large-scale discovery while maintaining data governance. Dr. Coutts will focus on machine learning models predicting treatment response and clinical outcomes in psychosis, with attention to generalizability, fairness, and real-world clinical implementation. Dr. Voppel will present emerging work on multimodal speech-based biomarkers for detecting clinically impairing thresholds of psychiatric symptoms, integrating acoustic, syntactic, and sentiment features to advance objective measurement in schizophrenia and related disorders.

This session brings together investigators across psychiatry, neuroscience, and artificial intelligence, spanning institutions and across career stages including early career investigators. By integrating predictive models, data platforms, generative systems, and multimodal

biomarkers, this symposium aligns with CCNP priorities and addresses urgent challenges in the safe, equitable, and effective deployment of AI in mental health care.

Speaker 1: Dr. Venkat Bhat, AI for Mental Health (AI-M) Program, Department of Psychiatry, University of Toronto; Unity Health Toronto, Toronto, ON, Canada

Title: ***"****Generative AI in Psychiatry: Clinical Applications and Implementation Challenges"*

Summary: Dr. Bhat will present emerging applications of generative AI in psychiatry, including conversational agents, clinical decision support tools, and multimodal data integration. He will highlight how these technologies can enhance measurement-based care and enable personalized treatment strategies. The talk will also address key challenges related to safety, regulation, and integration into clinical workflows. Examples from ongoing clinical and translational programs will be discussed.

Speaker 2: Dr. Tristan Glatard, Centre for Addiction and Mental Health (CAMH); University of Toronto, Toronto

Title: *"The Brain Health Data Challenge Platform: Enabling Scalable and Reproducible AI Research in Psychiatry"*

Summary: Dr. Glatard will present the Brain Health Data Challenge Platform as a large-scale infrastructure integrating neuroimaging, clinical, and biological data for AI research. He will highlight methods for reproducible and federated data analysis that enable scalable discovery while preserving privacy. The talk will address challenges in data harmonization and infrastructure design. Applications demonstrating acceleration of translational research will be discussed.

Speaker 3: Dr. Fiona Coutts, Centre for Addiction and Mental Health (CAMH); University of Toronto, Toronto

Title: *"From Prediction to Clinical Utility: Machine Learning Models in Psychosis"*

Summary: Dr. Coutts will present machine learning models predicting treatment response and clinical outcomes in psychosis using large, multi-cohort datasets. She will demonstrate model performance, external validation, and robustness across subgroups. The talk will emphasize clinical utility frameworks, including calibration and decision curve analyses, alongside fairness considerations. Implications for implementation in real-world psychiatric care will be discussed.

Speaker 4: Dr. Alban Elias Voppel, Douglas Mental Health Institute, McGill University, Montreal

Title: *"Multimodal Speech Markers for Detecting Clinically Impairing Psychiatric Symptoms"*

Summary: Dr. Voppel will present a multimodal approach to identifying clinically impairing thresholds of psychiatric symptoms using speech data from 319 participants, including individuals with schizophrenia spectrum disorders and healthy controls. He will demonstrate how acoustic, syntactic, and sentiment-based features can differentiate negative and depressive symptoms with high accuracy, including strong classification performance for negative

symptoms. The work emphasizes detection of functionally impairing symptom levels, enhancing clinical relevance beyond symptom presence alone. Implications for scalable, objective measurement and real-world clinical monitoring in schizophrenia will be discussed.

CCNP NEXT GENERATION SYMPOSIUM

Thursday, September 23 - (Abstracts chosen for Oral Presentations)

Chair: Dr. Jerome Foo (University of Alberta)

1. **A novel pharmacogenomics (PGx) panel for accurate and efficient detection of multiple types in a single workflow**

Jerome Clifford Foo, PhD [1,2], Ayokunnumi Ososami, BSc [2], Xiuying Hu, BM, MSc [1], Jiahui Liu, MD, PhD [1], Laiji Li, PhD [3], Katherine J. Aitchison BM BCh, PhD, FRCPsych[1,2,4,5] [1] Department of Psychiatry, College of Health Sciences, University of Alberta, Edmonton, Alberta, Canada [2] Neuroscience and Mental Health Institute, University of Alberta, Edmonton, Alberta, Canada [3] Department of Biochemistry, College of Health Sciences, University of Alberta, Edmonton, Alberta, Canada [4] Department of Medical Genetics, College of Health Sciences, University of Alberta, Edmonton, Alberta, Canada [5] The Psychiatry Section, Division of Clinical Sciences, Northern Ontario School of Medicine, Thunder Bay, Ontario, Canada

Introduction: Pharmacogenomic (PGx) testing is slowly gaining traction in clinical care. However, widespread implementation, especially at scale, has been challenging due to factors such as limitations in accuracy and range of variant coverage, expense, and the labour-intensive nature of sample preparation and result interpretation. Various pharmacogenes, including the hypervariable CYP2D6, which encodes an enzyme responsible for metabolizing ~20-25% of commonly prescribed drugs, are involved in drug metabolism; alterations of metabolism accompanying genetic polymorphisms make them crucial targets for PGx study.

Methods: The present study assessed the accuracy of concurrent single nucleotide polymorphism (SNP), copy number variants (CNV) and short sequence repeat (STR) detection by a novel comprehensive PGx panel using the Standard BioTools BiomarkTM X9 System for High-Throughput Genomics. The panel comprises 96 assays detecting variants in 11 pharmacogenes (CYP2D6, CYP2C19, CYP2C9, CYP2B6, CYP3A4, CYP3A5, CYP1A2, UGT1A1, HLA-A, HLA-B, and ABCB1), and CNV detection for CYP2D6. This included several novel assays, for example a custom CNV assay for detecting the CYP2D6 to CYP2D7 Exon 9 conversion. 95 clinical samples with prior consensus data from the Genome-Based Therapeutic Drugs for Depression (GENDEP) study were used. Concordance rates with expected SNP and CNV calls were calculated.

Results: Concordance with consensus genotypes was high for the majority of assays for both SNPs (>99%) and CYP2D6 CNVs, including promising findings for the novel Exon 9 conversion assay.

Conclusions: Preliminary findings are encouraging for the above targets, suggesting that the technology functions well.

2. The Neurobiological Effects of Psilocybin in Treatment Resistant Bipolar Depression

Erica S. Kaczmarek, Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada Nelson B. Rodrigues, Department of Psychology, University of Windsor, Windsor, Ontario, Canada Zoe Doyle, University Health Network, Toronto, Ontario, Canada Maya Stern, University Health Network, Toronto, Ontario, Canada Noah Chisamore, Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada Danica Johnson, Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada Colin Hawco, Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada Ishrat Husain, Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada Joshua D. Rosenblat, Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada

Introduction: Bipolar Disorder (BD) is a severe, chronic mental illness affecting 2-3% of the population. Depressive episodes are predominant, yet treatment options remain limited. Approximately one-third of patients fail to respond to two or more first-line treatments (treatment-resistant bipolar depression, TRBD), highlighting the need for novel therapeutics and an improved understanding of BD's neurobiology.

Methods: This open-label clinical trial investigates psilocybin-assisted psychotherapy (PAP) in TRBD. Participants (14 enrolled; target 20) with Bipolar II Disorder experiencing a moderate-to-severe depressive episode, and inadequate response to =2 treatments, receive a 25 mg dose of psilocybin with psychotherapy. Clinical outcomes were evaluated by assessing changes in depressive symptoms following treatment. The primary clinical endpoint was change in Montgomery Asberg Depression Rating Scale (MADRS) scores from baseline to Week 1, and a secondary endpoint at Week 4 evaluates durability of response. Neurobiological measures were also collected as part of the broader study but are not the focus of the present analysis. This trial is registered (NCT06506019).

Results: Recruitment is ongoing (n=17), with completion expected in July 2026. Interim analyses show a significant reduction in MADRS scores from baseline (30.6 ±6.8) to Week 1 (15.1 ±11.9; mean difference -15.5, p=0.0003), sustained at Week 4 (mean difference -16.6; p=0.0006). No treatment emergent mania, hypomania or psychosis was observed. Updated analyses will be complete prior to the conference.

Conclusions: PAP was associated with rapid and sustained reductions in depressive symptoms in TRBD, with no observed treatment-emergent mania, hypomania, or psychosis. These findings support the feasibility, safety, and potential antidepressant effects of PAP in Bipolar II depression.

3. Glutamate, glutathione, and GABA in chronic schizophrenia: a 7T DANTE-PRESS study of neurochemical correlates of symptom severity

Kesavi Kanagasabai[1,2,3], Michael Mackinely[3], Omer Oran[4], Jean Théberge[1,2,5], Lena Palaniyappan[1,2,3],6 [1]. Imaging Program, Lawson Research Institute, St. Joseph's Health Care London, ON, Canada. [2]. Department of Medical Biophysics, Western University, London, ON, Canada. [3]. Robarts Research Institute, Western University, London, Ontario, Canada. [4]. Siemens Healthcare Limited, Oakville, Ontario, Canada [5]. Department of Medical Imaging, St. Joseph's Health Care London, ON, Canada. 6. Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Montreal, Quebec, Canada.

Introduction: Schizophrenia is a complex psychiatric disorder that has been linked to disruptions in glutamatergic, GABAergic and redox systems. There is converging evidence that glutamate (Glu), gamma-aminobutyric acid (GABA) and glutathione (GSH) could be related to symptom expression (positive, negative, and/or cognitive) and disease progression. Single-voxel 1H-MRS is a non-invasive in vivo brain imaging technique used to quantify the concentration of psychiatric biomarkers. Conventional MRS technqiues produce complex spectra with overlapping resonances, limiting quantification reliability, while spectral-editing approaches require longer acquisition times and suffer from reduced signal-to-noise efficiency.

Methods: To address these limitations, we developed double-Delays-Alternating-Nutation-Tailored-Excitation-Point-RESolved-Spectroscopy (DANTE-PRESS), a novel single-shot multi-frequency-selective sequence that enhances metabolite specificity by suppressing out-of-passband signals while preserving resonances withing the DANTE passband. The objective of this study was to evaluate Glu, GSH, and GABA differences and their associations with clinical and cognitive measures in chronic schizophrenia. Twenty patient-volunteers living with chronic schizophrenia and twenty matched-healthy-volunteers were recruited for this study. All scans were performed on the Siemens-MAGNETOM 7T Plus (Erlangen, Germany) with an 8-transmit-channel/ - 32-receive-channel head-only radiofrequency-coil at the CFMM in London, Canada. Measurements of Glu, GABA, and GSH were obtained using DANTE-PRESS from the ACC.

Results: Using DANTE-PRESS, group mean %CRLB were <6%, <16%, and <12% for Glu, GSH, and GABA respectively with an average linewidth of ~10Hz. GSH levels were reduced in patients (Cohen's d=0.84, p=0.018, q=0.053) even after controlling for substance use (p=0.012). Among healthy controls, alcohol-consumers had lower GSH (p=0.009, d=1.48). Glu levels were negatively correlated with symptom severity (BNSS, PANSS-negative/general); non-significant negative trends observed for GABA (PANSS-negative/general/total and BNSS) and GSH (PANSS-negative and BNSS).

Conclusion: Our findings where reduced levels of GSH among patients are consistent with prior evidence of redox dysregulation in schizophrenia supporting the continued impaired antioxidant capacity. DANTE-PRESS provides a promising framework for developing robust, multi-metabolite imaging biomarkers in psychiatric disorders.

4. Have we asked the rats? Investigating individuality in polydrug self-administration patterns in rats

Adiia P. Stone, BSc.[1,2], Davin R. Peart, MSc. [1,2], Jessica M. Karlovcec, MSc. [1,2], Ana Barco [1], Charlotte E. Sfiligoi [3] Anita Sikic, MSc. [1,2], Ella V. Claridge, BSc. [1,2], Rita El Azali, BAS [1,2], Karim Abou El Naga, MSc. [1,2], Scott T. Barrett, PhD. [4], Jennifer E. Murray PhD.[1,2] [1]Department of Psychology, University of Guelph, Guelph, ON, Canada [2]Collaborative Neurosciences Graduate Program, University of Guelph, Guelph, ON, Canada [3]Department of Molecular and Cellular Biology, University of Guelph, ON, Canada [4]Department of Psychology, University of Nebraska – Lincoln, Lincoln, NE, USA

Introduction: ‘Speedballing’, the polydrug combination of cocaine (COC) and opioids such as fentanyl (FENT), is a rising public health crisis contributing to the high rates of Canadian overdose deaths. ‘Speedballing’ is reported to produce enhanced euphoria and be more reinforcing than single drug use, aligning with the synergistic increase in extracellular dopamine seen in rats self-administering opioid-stimulant cocktails. In humans, polydrug intake is highly individual, and relies heavily on personal preferences. Recently, this individuality in polydrug preference has also been demonstrated in rats with concurrent intravenous (IV) methamphetamine and fentanyl access, influencing reinstatement behaviours and preferences which are thus conserved when reinforcer value is manipulated. However, little is known about individuality in intake patterns of concurrent FENT and COC, their associated relapse-related behaviours post forced abstinence (ABS), and their sensitivity to drug-value manipulations.

Methods: Male and female rats underwent dual jugular vein catheterization before acquiring concurrent IV self-administration of COC (0.5 mg/kg/infusion) and FENT (2.5 µg/kg/infusion). After forced ABS, a subset of rats underwent various relapse tests (cued, uncued, and drug-primed). A second set of rats underwent dose challenge cycles, each manipulating the value of the reinforcer to assess behavioural sensitivity.

Results: Overall, rats reliably responded on both the fentanyl and cocaine levers. We used finite mixture models to investigate representation of subpopulations in our sample relating to polydrug self-administration. We found three distinct subpopulations of drug preference (BF_{10} = 5.60 and two distinct subpopulations of burst-like lever responding (BF_{10} = 6.69). Furthermore, drug preference during self-administration predicted later relapse-like behaviour (BF_{10} > 100).

Conclusions: Modelling individual preferences in stimulant versus opioid availability will help uncover mechanisms driving such preferences providing invaluable insight into polydrug use in human populations.

POSTER PRESENTATIONS

Friday, September 25

(listed alphabetically by presenters' names and in bold)

Congratulations to the following who are recipients of the W. G. Dewhurst Travel Award:

Sara Asgharzadeh, University of Ottawa
Christian Ramos-Jiménez, McGill University
Haley Vecchiarelli, University of Guelph

1. Robust Brain Connectivity Predictors of Response to Brain Stimulation Treatment for Major Depression: Generalizability Across CARTBIND and THREE-D Clinical Trials.

Rhea Agarwal, BSc[1] Daniela Giansante, BSc[1,2] Bailey Ng, MSc[1,2] Hassan Abdulrasul, MSc[1,2] Thomas Tan, MSc[1] Zafiris J. Daskalakis, MD, PhD[4] Jonathan Downar, MD, PhD[2,3] Fidel Vila-Rodriguez, MD, PhD[5] Diego A. Pizzagalli, PhD6 Daniel M. Blumberger, MD[1,2,3] Peter Zhukovsky, PhD[1,2,3] [1] Centre for Addiction and Mental Health, Toronto, ON, Canada [2] Institute of Medical Science, University of Toronto, Toronto, ON, Canada [3] Department of Psychiatry, University of Toronto, Toronto, ON, Canada [4] Department of Psychiatry, University of California San Diego, San Diego, CA, United States [5] Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada 6 Department of Psychiatry, University of California Irvine School of Medicine, Irvine, CA, United States

Introduction: Over one-third of patients with major depressive disorder do not respond to frontline treatments and receive alternative treatments such as repeated transcranial magnetic stimulation (rTMS). Biomarker discovery and validation across distinct clinical trials is needed to identify those who are most likely to benefit from rTMS.

Methods: The study used data from individuals with treatment-resistant depression enrolled in CARTBIND (n = 174) and THREE-D (n = 212) clinical trials. CARTBIND used intermittent theta-burst stimulation (iTBS), whereas THREE-D administered both iTBS and traditional rTMS. Functional connectivity of the left dorsolateral prefrontal cortex (dlPFC), dorsal and ventral anterior cingulate cortex (dACC, vACC) with 360 cortical regions alongside clinical and demographic information were tested as predictors of treatment response (=50% reduction in Hamilton Rating Scale for Depression score from baseline). An elastic net regression model with 10-fold nested cross-validation was used to predict response in THREE-D; models were then trained in THREE-D and tested in CARTBIND and vice versa.

Results: Participants in both cohorts were comparable in demographic characteristics, including age and sex (CARTBIND: mean(SD) age = 41.4 (11.4), 66.1% female; THREE-D: mean(SD) age = 41.8(11.3), 62.7% female). Models trained and tested on THREE-D demonstrated strong performance in cross-validation (left dlPFC AUC=0.879, dACC AUC=0.709, vACC AUC=0.654), with neuroimaging variables improving prediction compared to clinical data alone (AUC=0.536).

The model including clinical data and the left dlPFC connectivity showed robust predictive performance across trials (Train on THREE-D, Test on CARTBIND AUC=0.643; Train on CARTBIND, Test on THREE-D AUC=0.657).

Conclusion: These findings suggest functional connectivity of the left dlPFC is a predictive marker for rTMS response in treatment-resistant depression. Future studies should include additional rTMS trials and other MDD treatment modalities in search of biomarkers predicting treatment response.

2. Role of Protocadherin-alpha in Fluoxetine-induced Recovery of Serotonergic Circuitry and Hippocampal Neurogenic Maturation Following Stroke

Sara Asgharzadeh[1,2], Faranak Vahid-Ansari[2], Mireille Daigle[2], Paul R. Albert[2] [1]Neuroscience Graduate Program, Cellular and Molecular Medicine, University of Ottawa, [2]Ottawa Hospital Research Institute (Neuroscience) and, Brain and Mind Research Institute, University of Ottawa, Ottawa, ON, Canada

Introduction: Post-stroke depression (PSD) is prevalent after stroke and is associated with anxiety, depression and cognitive impairment. Selective serotonin reuptake inhibitors, such as fluoxetine (FLX), can improve PSD outcomes, but remission is incomplete, and the circuit mechanisms underlying recovery remain unclear. In a PSD mouse model of focal ischemia in the left medial prefrontal cortex (mPFC), chronic FLX restores behavioral function and serotonergic innervation. Because protocadherin-aC2 (PcdhaC2) is important for developmental serotonergic axonal organization, we investigated whether FLX-mediated recovery requires PcdhaC2 for restored serotonergic postsynaptic connectivity and hippocampal neurogenic plasticity.

Methods: Mice given endothelin-1-induced left mPFC stroke were treated with chronic FLX or vehicle. Behavioral and cognitive performance were assessed using multiple anxiety, depression, and memory-related tests. In Pcdha-wild-type (WT) and 5-HT neuron-specific conditional knockout (Pcdha-cKO) mice, hippocampal neurogenesis was evaluated by quantifying doublecortin (DCX)-positive neurons and dendritic morphology in the dentate gyrus. To assess serotonergic synaptic connectivity, AAV1-Cre that can cross a synapse was injected into the dorsal raphe nucleus of ROSA-YFP reporter mice, and postsynaptic targets were identified by GFP labeling and colocalization with CaMKIIa and GAD67 across forebrain regions.

Results: FLX improved anxiety-, depression-, and cognitive-like behaviors in WT PSD mice, whereas these effects were absent in Pcdha-cKO mice. In the dentate gyrus, DCX-positive cell numbers were unchanged; however, dendritic complexity was reduced in Pcdha-cKO mice under basal conditions and further impaired after stroke. FLX significantly increased dendritic length and branching in WT but not cKO mice. In ROSA-YFP mice, AAV1-Cre tracing revealed that stroke reduced postsynaptic GFP labeling in ipsilesional cortical and hippocampal regions. FLX increased total GFP-positive cells and restored targeting to both excitatory (CaMKIIa+) and inhibitory (GAD67+) neurons.

Conclusion: These findings demonstrate that FLX-mediated behavioral recovery after stroke involves coordinated improvements in serotonergic circuit reinnervation and hippocampal neurogenic maturation that involve PcdhaC2-mediated axonal outgrowth.

3. Lower TREM2 expression and Altered Microglial Morphology in Prefrontal Cortex in Bipolar Disorder: Association with Synaptic Density

Sangeetha Kasturi, MSc, Christa Hercher, PhD, Li Shao, PhD, **Clare L Beasley** PhD
Department of Psychiatry, University of British Columbia, Canada

Introduction: Microglia are the principal immune cell within the brain parenchyma. Recent studies suggest that, in addition to immune functions, these cells embrace diverse roles in normal brain development and maintenance, including modulation of synaptic plasticity. The microglial receptor TREM2 is a critical regulator of microglial activity, facilitating their ability to sense and respond to damage, as well as mediating interactions with synapses and supporting energy metabolism. While alterations in microglia and their associated transcripts have previously been reported in bipolar disorder (BD), findings are inconclusive. The role of TREM2 in mediating microglial reactivity and synaptic maintenance has not yet been explored in this disorder. As such, the aims of this study was to investigate TREM2 expression and microglial morphology in BD, as a proxy of microglia functional state, and to examine associations with synaptic density.

Methods: Protein and mRNA expression of TREM2 was quantified in postmortem prefrontal cortex in BD (n = 34) and matched controls (n = 35) using Western blotting and quantitative PCR. The density of microglial morphological subpopulations was quantified by immunohistochemistry. The pre-synaptic protein SNAP-25 was quantified by enzyme linked immunosorbent assay.

Results: Both TREM2 protein and mRNA expression were lower in BD relative to controls. The density of microglia with 'reactive' morphologies was lower in BD compared to controls. Correlations were observed between TREM2 expression, microglial density and SNAP-25 protein levels.

Conclusion: Our results implicate microglia and the microglial receptor TREM2 in the pathophysiology of BD, being suggestive of a failure of immune surveillance rather than active inflammation. It could be postulated that lower TREM2 expression in BD may inhibit microglial activation. Further research is needed to explore microglial state in this disorder and delineate the role of microglia in mediating synaptic plasticity.

4. Precision Functional Magnetic Resonance Imaging in Psychosis Spectrum Disorders: Feasibility and Connectome Fingerprinting

Mohammad Chaposhloo, Ph.D [1]; Lindsay Oliver, Ph.D [1,2]; Ju-Chi Yu, Ph.D [1]; Ruyi Pan [1,3]; Javkhlan Byambadorj [1]; Suddene Stone [1]; Ghazaleh Mohammadalinejad, MSc [1]; Mahavir Agarwal, M.D., Ph.D [1,2]; George Foussias, M.D., Ph.D [1,2]; Margaret Hahn, M.D., Ph.D [1,2]; Kathleen Bingham, M.D., Ph.D [2, 4]; Benoit Mulsant, M.D., M.Sc [1,2]; Alastair Flint, M.D. [2, 4]; Aristotle Voineskos, M.D., Ph.D [1, 2, 4]; Colin Hawco, Ph.D [1,2]; Nicholas Neufeld, M.D., M.Sc [1,2] [1]. Centre for Addiction and Mental Health, Toronto, Ontario, Canada [2]. Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada [3]. Department of Statistical Sciences, University of Toronto, Toronto, Ontario, Canada [4]. University Health Network, Toronto, Ontario, Canada

Introduction: Heterogeneity in individuals with psychosis limits the clinical utility of group-averaged neuroimaging studies. Precision functional magnetic resonance imaging (pfMRI)

offers an alternative by leveraging multiple and longer scans to obtain reliable and individualized biomarkers. However, the feasibility of pfMRI in individuals with psychosis remains untested. This study aimed to investigate a) whether it is feasible to collect high-quality pfMRI data from a relatively large sample of participants with schizophrenia spectrum disorders (SSDs), remitted psychotic depression (rPD) and controls, and b) whether individuals would show unique and identifiable brain patterns.

Methods: Across 12 weeks, participants completed biweekly sessions of resting-state fMRI (14-35 minutes each) and ratings of general psychiatric and depressive symptoms. Recruitment, retention, and data quality were assessed. Following preprocessing, nuisance regression, and individualized brain parcellation, pairwise functional connectivity and correlations between all session pairs were calculated.

Results: Across SSDs, rPD, and Control groups, n=14/8/9 participated in pfMRI scanning; n=10/8/8 completed all six sessions; n=4/0/1 partially completed. In total, 171 sessions were completed, yielding an average of 159.6 minutes of resting-state fMRI data for each participant. Motion during scanning (mean framewise displacement; FD) was low (SSDs=0.20, rPD=0.20, Controls=0.15 mm). Retaining only time-points with FD < 0.5 mm, data loss was minimal (SSDs=7%, rPD=5%, Controls=4%). Compared to mean between-participant brain similarity (SSDs: r=.50, rPD: r=0.46, Controls: r=0.46), within-participant similarity was higher in SSDs (r=.80), rPD (r=.79), and Controls (r=.79).

Conclusion: Results demonstrate that pfMRI is feasible in patients with psychosis spectrum disorders and that using pfMRI can distinguish individual brain patterns.

5. The Association Between the Polygenic Risk Scores for Type II Diabetes and Grey Matter Structure in Youth with Bipolar Disorder

Natalie Chiang, BSc, Centre for Addiction and Mental Health, University of Toronto Nidhi Kulkarni, PhD, MSc, Centre for Addiction and Mental Health, Clement Zai, PhD, MSc, Centre for Addiction and Mental Health, Kody Kennedy, PhD, BSc, Centre for Addiction and Mental Health, Megan Mio, PhD, BMSc, Centre for Addiction and Mental Health, Trevor L. Young, MD, PhD, Centre for Addiction and Mental Health, University of Toronto Bradley MacIntosh, PhD, MSc, Sunnybrook Research Institute, University of Toronto Benjamin Goldstein, MD, PhD, FRCPC, Centre for Addiction and Mental Health, University of Toronto

Introduction: Bipolar disorder (BD) is associated with an increased risk of Type 2 Diabetes Mellitus (T2DM), which are both polygenic conditions that are associated with anomalous grey matter structure. The present study examined the association of polygenic risk scores for T2DM (T2DM-PRS) with grey matter metrics in youth with and without BD.

Methods: In a study of 109 youths and young adults (mean age: 17.2 years; n=64 BD, n= 45 controls), participants underwent T1-weighted magnetic resonance imaging. T2DM-PRS were calculated using independent, adult genome-wide association summary statistics. The main effect of T2DM-PRS on grey matter metrics in the anterior cingulate cortex (ACC) and hippocampus was examined using covariate-adjusted general linear models. PRS-by diagnosis interaction and sex-stratified analyses were also conducted. Sensitivity analyses controlled for psychotropic medications, traditional cardiovascular risk factors, and all 10 genetic principle components.

Results: Higher T2DM-PRS was associated with significantly higher ACC volume (ß=0.25, p=0.04) and surface area (ß=0.26, p=0.02), within the BD group only. These findings were significant in females but not males. There was a significant PRS-by-diagnosis interaction effect (ß=0.15, p=0.03) whereby higher T2DM-PRS was associated with higher ACC area within the BD group but not controls. All primary findings remained significant in sensitivity analyses (except when controlling for antipsychotics and lithium) and additional findings emerged.

Conclusion: Although present findings support an association between T2DM-PRS and brain structure in youth with BD, particularly in females, the direction of these findings was unexpected. Future studies evaluating sex differences, medication classes, and comprehensive covariate modeling are warranted.

6. Efficacy, safety and tolerability of lysergic acid diethylamide for the treatment of depressive symptoms: A meta-analysis and systematic review

Andreea Chiorean, Helena Kim Andrew Lustig Ishrat Husain

Introduction: Since the Food and Drug Administration designated lysergic acid diethylamide (LSD) as a “breakthrough” treatment for generalized anxiety disorder, accumulating randomized clinical trials (RCTs) evaluating LSD’s anxiolytic effects have also reported improved depression symptoms. Given the co-occurrence of anxiety and depression, evaluating the safety and efficacy of LSD in treating depression symptoms is warranted.

Methods: MEDLINE/PubMED, Embase, and PsychINFO were searched from inception to December 9, 2025. RCTs evaluating efficacy of LSD on depression symptoms in adults with mental disorders were included. Cochrane Risk of Bias Tool 2.0 and X2 and I2 tests were used to measure quality and heterogeneity. This review was preregistered on PROSPERO (CRD420251063539).

Results: Of 465 screened studies, five RCTs met selection criteria (N = 227). Our synthesis and random-effects meta-analysis demonstrated that LSD treatment significantly reduced depression symptoms compared to the comparator (SMD = -0.65; 95% CI: -0.92 to -0.38, p = 0.000002). Studies varied in design and three of the included studies administered LSD with psychological support, although study-level heterogeneity was not significant (I2 =0%, p = 0.54). Three studies had low risk of bias. All-cause discontinuation demonstrated reasonable acceptability of LSD treatment. Severe adverse events possibly related to study parameters included hospitalizations (N = 3) and acute anxiety/delusions (N = 1).

Conclusion: Our findings suggest that LSD, with and without psychological support, reduces depression scores in clinical populations. This review is limited by small sample size. Future well-designed RCTs are needed to establish the efficacy and safety of LSD in managing depression.

7. Evaluating the Effects of Concomitant Medications on the Antidepressant Efficacy of Ketamine: A Secondary Analysis of a Randomized, Midazolam-Controlled Clinical Trial of Treatment-Resistant Bipolar Depression

Noah Chisamore, HBSc[1,2], Diana Orsini, MSc, MPH[1,2], Sara Di Luch, BHSc[1,2], Shreya Vasudeva, HBSc[1,3], Gabrielle Lovell, BMSc[1,3], Danica Johnson, BScH[1,3], Erica Kaczmarek, HBSc[1,2], Rodrigo Mansur MD, PhD[1,3], Roger McIntyre, MD[3,5] Amer Burhan MBChB, MSc[4],6, and Joshua Rosenblat, MD, MSc, FRCPC[1,2,3,4] Affiliations: [1]. Poul Hansen Family Centre for Depression, University Health Network, Toronto, ON, Canada [2]. Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada [3]. Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada [4]. Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada [5]. Brain and Cognition Discovery Foundation, Toronto, Ontario, Canada 6. Ontario Shores Centre for Mental Health Sciences, Whitby, ON, Canada

Introduction: Bipolar disorder (BD) presents significantly elevated risks of psychiatric comorbidities, chronic medical conditions and mortality. Unfortunately, over 25% of BD patients do not respond to at least two treatments, and are considered treatment-resistant (TRBD). Though intravenous ketamine has rapid and pronounced antidepressant effects, there is a lack of research of IV ketamine for bipolar depression. Psychiatric medications often used in BD, particularly anticonvulsant drugs, may pharmacodynamically interact with ketamine, prompting an analysis of how these drugs affect the antidepressant efficacy of ketamine in TRBD

Methods: The parent trial (Ket-BD: NCT05004896) was a randomized, placebo controlled, clinical trial investigating four infusions over two weeks of either ketamine or midazolam (psychoactive-control) to evaluate antidepressant efficacy, safety, and tolerability in TRBD. The Montgomery–Åsberg Depression Rating Scale (MADRS) was used to evaluate depression symptoms over time until two days post-infusion four at Day 14, and at Day 28. Linear mixed models were used to evaluate if concomitant use of lamotrigine, lithium or benzodiazepines influenced depression symptoms over time by treatment arm.

Results: There was a significant effect of treatment arm ($p=0.017$), time ($p<0.001$) and baseline MADRS ($p<0.001$) on MADRS over time, favouring ketamine over midazolam. Concomitant use of lamotrigine, lithium or benzodiazepines and number of concomitant anticonvulsants did not significantly influence the response to ketamine. The combined effect of lamotrigine, lithium and benzodiazepine use irrespective of treatment arm was also insignificant.

Conclusions: Concomitant medication use did not attenuate the antidepressant efficacy of serial ketamine infusions. Practitioners should still consider possible interactions of ketamine with psychiatric medications as antidepressant effects can still occur with concomitant use of GABAergic drugs such as lamotrigine and benzodiazepines, and mood stabilizers like lithium Future clinical trials should continue to evaluate the efficacy and safety of these medications in conjunction with IV ketamine.

8. Real-time serotonin dynamics in the mesolimbic dopamine system track motivational demand and reward uncertainty

Mya Z. Chronopoulos, BHSc[1,2]; Paul S. Jung, BHSc, MSc[1]; Zhaoxia Li, MSc[1]; Emerson Hamilton[1]; Caleb J. Browne, BSc, MA, PhD[1,2,3,4]

Introduction: Motivation enables organisms to initiate and sustain goal-directed behaviour necessary for survival. Dysregulation of motivational processes underlies many major psychiatric conditions, most notably depression. While the mesolimbic dopamine system is well established as a core driver of motivated behaviour, the role of serotonin within this circuit remains poorly understood. Prior studies have examined serotonin's contribution using broad

manipulations of serotonin function, but the real-time dynamics that coordinate motivated behaviour remain unknown. To address this gap, we investigated real-time serotonin activity within the nucleus accumbens (NAc) during motivated behaviour.

Methods: In vivo fiber photometry, combined with operant responding for water in mice, was used to monitor serotonin release. Mice received stereotaxic delivery of a genetically encoded serotonin sensor (AAV9-hSyn-GRAB-5-HT3.0) and optic fiber implantation targeting the NAc. Following recovery, animals progressed through an escalating paradigm of reinforcement schedules designed to systematically increase motivational demand and reward uncertainty. Serotonin signals were normalized, aligned to lever pressing and reward delivery, and analyzed for peri-event changes using an area under the curve approach.

Results: Across reinforcement schedules, we observed a consistent pattern of serotonergic activity – an initial spike in serotonin release at the time of lever pressing, followed by a reduction during reward consumption, and a rebound in activity upon completion of reward consumption. Notably, the amplitude of serotonin modulation during the reward phase scaled with reinforcement uncertainty.

Conclusions: These findings suggest that serotonin signaling in the mesolimbic dopamine system is tightly coupled to motivated behaviour. Ongoing studies will further examine serotonin dynamics within the ventral tegmental area and refine the causal contributions of serotonin to motivational control. Together, this will advance our understanding of neuromodulatory regulation of goal-directed behaviour and lay critical groundwork for understanding motivational dysfunction in psychiatric disorders.

9. Assessing the discriminative stimulus properties of naloxone through Pavlovian associative learning

Ella Claridge, Jessica Karlovcec, Davin Peart, Adiia Stone, Anita Sikic, Jiayu Zheng, Teena Sharma, Charlottle Sfiligoi, Jennifer Murray

Introduction: Interoceptive drug stimuli can acquire conditioned modulatory properties resulting in conditioned appetitive behaviours by exteroceptive reward cues in a Pavlovian drug discrimination task. Occasion setting (OS) relies heavily on intrinsically rewarding stimuli to create strong associations, but little is known about the behavioural patterns of aversive stimuli in this task. Naloxone (NLX), a mu opioid receptor antagonist, conditions a place aversion in both opioid-dependent and naïve animals and therefore has the potential to effectively function as an OS despite being intrinsically aversive.

Methods: Male and female rats underwent 32 sessions of OS under 3 training contingencies with NLX (1mg/kg) and saline: feature positive (FP), where the drug stimulus is trained to disambiguate when an exteroceptive light conditioned stimulus is followed by the unconditioned stimulus, sucrose; feature negative (FN), where the opposite contingency is true; and control (FX), where access to sucrose is random and not dependent on drug treatment. Following OS training, all animals underwent 11 sessions of NLX place conditioning (PC) Test sessions had freely roaming animals explore both sides without drug administration.

Results: NLX did not effectively function as an OS at 1mg/kg and conditioned a place aversion at final test even after appetitive training with sucrose.

Conclusions: The biphasic antagonistic effects of NLX likely blocked the acquisition of behaviour in OS while enhancing expression of aversive behaviours in PC.

10. Synaptic Density in Youth With Regular Cannabis Use: A [18F]SynVesT-1 PET Imaging Study

Cassie Côté, HBSc ([1,2]); Maia Zilberman, HBSc ([1,2]); Shahtaj S. Dheda, HBSc ([1,2]); Vivian Mohn, HBSc ([1,2]); Khalid Manji, MBBS ([2]); Kelly Smart, PhD ([3]); Kimberly Desmond, PhD ([1,2]); Dafna Kahana, MD ([1,2]); Bernard Le Foll, MD ([1,2]); Yuliya Nikolova, PhD ([1,2]); Neil Vasdev, PhD ([1,2]); Tina McCluskey, MSc ([2]); Jerry Warsh, PhD ([1,2]); Omair Husain, MD ([1,2]); and Isabelle Boileau, PhD ([1,2]).

Introduction: Adolescence is a critical period for neurodevelopment, marked by synaptic pruning. Lower synaptic density has been reported in adults with chronic cannabis use1-2 but it remains unclear if this is seen in youth. Here, we investigate if regular cannabis exposure in youth is related to lower synaptic density using [18F]SynVesT-1 PET.

Methods: A preliminary sample of healthy youth (16-26 years) underwent [18F]SynVesT-1 PET scan. MRI scans were used to delineate six corticolimbic regions of interest. Time-activity curves were fitted using a simplified reference tissue model (SRTM-2) with the centrum semiovale as a pseudo-reference region. Non-displaceable binding potential (BPnd) was compared. Cannabis use over the past 90 days (TLFB-90) classified participants as low (<1x/week) and regular (=1x/week) cannabis use. Use severity and pattern were assessed with CUDIT and DFAQ-CU.

Results: Forty individuals (22M, 18F, 22.3 years) completed PET imaging. Fifteen reported regular use of cannabis (10M, 5F; 23.1 years old; 5.1 years of regular use; 64±22 /90 days) and 25 reported low use (12M, 13F; 21.7 years; 3±4 /90 days). Among regular users, eleven met threshold for hazardous use (8+), and six for potential cannabis use disorder (CUD, 12+) (CUDIT: 11.7±5.9). No differences in synaptic density were observed between groups (-0.7% overall; p>0.05). There were also no differences observed between low users and those with potential CUD (+2.1% overall; p>0.05). No correlations with synaptic density were found with CUDIT or TLFB (respectively, ?=-0.035 to ?=-0.140; ?=-0.026 to ?=-0.092; p>0.05).

Conclusion: Our findings do not support differences in synaptic density between youth with regular vs. low cannabis use. This contrasts with prior findings of lower synaptic density in those with CUD, suggesting lower synaptic density may relate to more chronic, long-term exposure (~8 years of use). Further assessment of differences in synaptic density in youth with cannabis use is underway.

12. ERK Inhibition Reduces Audiogenic Seizure Susceptibility and Auditory Circuit Hyperexcitability in a Fragile X Mouse Model

Jordyn Crawford, BSc; Xiuping Liu, PhD; Evan Tigley, BSc; MoonYoung Bae, BSc; Jun Yan, PhD; Ning Cheng, PhD Neuroscience, University of Calgary, Calgary, Alberta, Canada

Introduction: Fragile X Syndrome (FXS) is the most common inherited cause of autism spectrum disorder and intellectual disability, with sensory hypersensitivity linked to hyperexcitability in central auditory circuits as a core feature. We aimed to determine whether

pharmacological inhibition of upregulated extracellular signal-regulated kinase (ERK) signaling using PD325901 (PD; mirdametinib), an FDA-approved drug for neurofibromatosis type 1, reduces auditory circuit hyperexcitability and rescues behavioral phenotypes in Fragile X messenger ribonucleoprotein 1 (FMR1) knockout (KO) mice.

Methods: FMR1 KO and wild-type (WT) mice (FVB background) were studied using acute and chronic PD treatment paradigms. For acute treatment, mice received a single intraperitoneal injection of PD (1, 10, or 25 mg/kg) or vehicle, followed by audiogenic seizure (AGS) testing 1 hour later at postnatal day 20 (P20). For chronic treatment, PD (5 mg/kg; 25 µg/mL in drinking water) or vehicle was administered via the dam from postnatal day 7 (P7), with AGS testing at P20. Acute in vivo electrophysiology was conducted in the central nucleus of the inferior colliculus (ICc) to assess auditory circuit excitability. Developmental milestones were evaluated from P2–P18.

Results: KO mice exhibited severe AGS phenotypes, including high seizure incidence and ~45% mortality. Acute PD treatment dose-dependently reduced AGS severity in KO mice, while chronic PD treatment markedly reduced AGS severity, increasing normal behavioral responses (~80%) and eliminating mortality. Acute PD administration also significantly reduced ICc firing in KO mice ($p = 0.0013$), with no effect observed in WT controls. Developmental assessments showed normal age-dependent progression with no treatment-related disruptions across groups.

Conclusion: ERK inhibition via PD reduces audiogenic seizure susceptibility and suppresses central auditory hyperexcitability in FMR1 KO mice following acute and chronic treatment without impairing development. These findings support ERK signaling as a contributor to sensory dysfunction in FXS and highlight PD as a promising translational candidate for targeting auditory hypersensitivity.

13. Lateral Stripe of the Striatum: Molecular Mapping, Functional Discourse, and Actionable next Steps in a Neglected Corner of D1 Activity

Erik Daroczi, PhD Candidate (Integrated Program in Neuroscience, McGill University, Douglas Mental Health University Institute, Montreal, QC, CA), Ghazal Fakhfouri, PharmD, PhD (Psychiatry, Douglas Mental Health University Institute, Montreal, QC, CA), Bruno Giros, PhD (Psychiatry, Douglas Mental Health University Institute, Montreal, QC, CA; Université de Paris, Paris, FR)

Introduction: The striatum is a well conserved brain region implicated in motor, reward, and cognition. Medium spiny neurons make up most of the striatum and are functionally divided by dopamine receptor expression (D1- or D2-MSNs). Despite this, modern transcriptomics reveal “atypical MSNs” which express unique combinations of molecules that complicate the D1/D2 functional binary. Recently, the lateral stripe of the striatum (LSS), a subregion enriched in atypical-D1-MSNs, was implicated in reward/aversion and motor control. However, the LSS’ small size, shrouded molecular characterization (unlabelled/merged in datasets), and few recognized genetic targets, has made further study difficult. Furthermore, current genetic LSS targets often also occur in adjacent striatal populations, further complicating targeting. To enable LSS research, this study aims to increase availability and flexibility of targets for the LSS through spatial mapping, identification, and validation of genes in mice.

Methods: Consistent LSS subtypes will be isolated from transcriptomic data and mapped to bregma locations. Using wildtype mice, the map will be validated via RNAScope™ on marker genes. Marker genes will be further filtered to identify targetable (spatially specific) genes. Targetable genes will be compared to lists of transgenic mouse strains to reveal available genetic tools for LSS targeting. Selected strains will be acquired and validated via RNAScope™.

Results: Preliminary analysis from a single dataset (8.5k genes, 174k cells, filtered against 1.7k strains) reveals 5 targetable LSS-associated genes with currently available mouse strains.

Conclusion: This study will identify tools for LSS exploration and targets for future tool development, thereby directing subsequent research with clarity. The verified LSS mapping will contribute accurate striatal topology and, because the striatum is conserved, influence human research.

14. Polygenic Risk for Suicide Attempts and Brain Structure in Youth with and at Risk for Bipolar Disorder

Mikaela K. Dimick, PhD, Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, Ontario, Canada Kody G. Kennedy, PhD, Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, Ontario, Canada Clement Zai, PhD, Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, Ontario, Canada Mojdeh Zamyadi, MSc, Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, Ontario, Canada Bradley J. MacIntosh, PhD, Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada, MD, PhD, Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, Ontario, Canada Benjamin I. Goldstein

Introduction: Youth with bipolar disorder (BD) are at greatly increased risk for suicide. Frontolimbic regions are implicated in suicide attempts among youth and adults. Polygenic risk scores (PRS) for suicide attempts have yet to be examined in relation to neuroimaging phenotypes in youth. This study examined associations between suicide-attempt PRS (SA-PRS) and brain structure in a controlled study of youth with or at risk for BD.

Methods: Participants were 139 youth of European ancestry with or at risk for BD (BD=84) and controls (n=55) who completed 3T MRI. Diagnoses and self-harm were ascertained via the K-SADS-PL. SA-PRS were computed using PRS-CS-auto. Amygdala volume and orbitofrontal (OFC) and ventrolateral prefrontal (vlPFC) cortical measures were derived using FreeSurfer. Vertex-wise and ROI analyses investigated PRS effects within BD and diagnosis-by-PRS interactions, adjusting for age, sex, genetic principal components, intracranial volume, and scanner.

Results: Higher SA-PRS was associated with larger amygdala volume in youth with BD (ß=0.31, p=0.02), and in a diagnosis x PRS interaction (ß=0.13, p=0.03). There were no OFC or vlPFC findings. Vertex-wise analyses identified several PRS x diagnosis and PRS x self-harm interactions in regions including the caudal ACC, insular, lateral occipital cortex, and prefrontal cortical regions (CWPs=0.008-0.04).

Conclusion: We report preliminary findings regarding neurostructural intermediate phenotypes of elevated polygenic risk for suicide attempt in BD. Taking together ROI and vertex-wise

analyses, implicated regions include the amygdala, insular and cingulate regions. Future larger studies with prospective designs are warranted to build on these findings.

15. Gray and white matter microstructures are associated with cognitive performance in treatment-resistant late-life depression

Clarize A Donato[1,2*]; JAE Anderson[3*] PhD; MA Butters[4], PhD; H Abdulrasul[1,2]; H Lavretsky[5], MD; PJ Brown6, PhD; JS Shimony7, MD, PhD; EJ Lenze8, MD; DM Blumberger[1,2], MD; AJ Flint[2],9, MD; JF Karp[10], MD; S Roose6, MD; K Conaty[4]; E Richard[11]; IX MacPhee[11]; JP Miller[12]; C Hawco[1,2], PhD; EW Dickie[1,2], PhD; BH Mulsant[1,2,13], MD; AN Voineskos[1,2†], MD, PhD; P Zhukovsky[1,2†], PhD [1]Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health [2]Department of Psychiatry, Institute of Medical Science, University of Toronto, Toronto, ON, Canada [3]Department of Psychology, Carleton University, Ottawa, ON, Canada [4]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA [5]Department of Psychiatry, University of California, Los Angeles, CA, USA 6Department of Psychiatry, Columbia University College of Physicians and Surgeons and the New York State Psychiatric Institute, New York, NY, USA 7Mallinckrodt Institute of Radiology, Washington University, St Louis, MO, USA 8Department of Psychiatry, Washington University, St Louis, MO, USA 9Centre for Mental Health, University Health Network, Toronto, ON, Canada [10]Department of Psychiatry, University of Arizona, Tucson, AZ, USA [11]Department of Cognitive Science, Carleton University, Ottawa, ON, Canada [12]Institute for Informatics, Data Science and Biostatistics, Washington University, St Louis, MO, USA [13]The Royal Ottawa Hospital, Ottawa, ON, Canada *co-first authors †co-supervised work

Introduction: Individuals with treatment-resistant late-life depression (TR-LLD) have varying levels of cognitive impairment and are at an increased risk for dementia. Neural correlates underlying cognitive dysfunction and treatment response in this population are not well understood. We investigated associations between grey and white matter microstructure with both cognition and depression treatment outcomes.

Methods: Older adults (Age>60) with treatment-resistant depression completed cognitive assessments and diffusion-weighted and T1 neuroimaging scans. The neurite orientation dispersion and density imaging (NODDI) model was used to derive microstructural indices of neurite density (NDI; the packing of neurites), orientation dispersion (ODI), and free water (isotropic volume fraction; fISO, where greater free water diffusion suggests atrophy) in grey and white matter. Associations between baseline NODDI indices and cognition were tested using linear regression models (n=195) with false discovery rate (FDR) correction for multiple comparisons. Regularized elastic net logistic regressions were used to predict remission from demographic, clinical, and NODDI data (n=150).

Results: NDI and ODI were not significantly associated with cognition (pFDR>0.05). Significant main effects of fISO on delayed memory were found in the left supramarginal gyrus, right pars orbitalis and insula, and inferior parietal cortex (pFDR<0.05). Greater fISO was associated with worse delayed memory. Mean fISO in an individualized inferior longitudinal fasciculus tract was negatively associated with delayed memory (p=0.0047). Addition of fISO (AUC=0.71) modestly improved remission prediction compared to demographic and clinical data alone (AUC=0.68) but performed worse than cortical thickness (AUC=0.79).

Conclusion: The findings of this study provide further evidence for fISO as a biomarker for cognitive impairment in older adults generally, and for the first time in those with TR-LLD, who

are at high risk for cognitive decline and dementia. Future studies are needed to address the relationship between fISO, cognitive impairment, and outcomes in TR-LLD.

16. Parsing punishment contingency: distinct behavioural phenotypes during oral morphine self-administration

Rita El Azali, BAS, Ava R. Noon, Adiia P. Stone, BSc, Siobhan Latremouille, Alexandria. McGinn, BAS, Davin Peart, MSc, Scott T. Barrett, PhD, Jennifer E. Murray, PhD Department of Psychology, University of Guelph, Guelph, ON, CAN Collaborative Neuroscience Program, University of Guelph, Guelph, ON, CAN Department of Biomedical Sciences, University of Guelph, Guelph, ON, CAN Department of Psychology, University of Nebraska, Lincoln, Nebraska, USA

Introduction: The present study investigates the individual differences that emerge as a result of contingent and non-contingent punishment on oral morphine (OM) seeking.

Methods: Male and female rats were randomly assigned to: Morphine Control (MC); Punishment (P); Yoked (Y); Shock Control (SC); and Chamber Control (CC). Following OM acquisition, groups transitioned to the punishment phase. MC rats continued self-administration (SA) with no foot shocks (FS). P rats received FS at a 15% probability, contingent on active lever pressing for OM. 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 OM; CC rats never experienced FS or had access to OM.

Results: MC males and females consumed similar morphine levels (mg/kg), stabilizing over time. Contingent FS reduced intake overall but revealed marked individual differences, distinguishing punishment-resistant and punishment-sensitive animals. In contrast, non-contingent FS did not reduce consumption. Females showed reduced pain sensitivity in the tail-flick test, and both sexes exhibited decreased sensitivity post-experiment relative to baseline.

Conclusion: This study provides a useful model for studying how adverse consequences differentially influence drug-seeking and insight into individual differences between those sensitive and resistant to punished seeking behaviour of a morphine solution.

17. Nicotine withdrawal alters ultrasonic vocalizations in adult rats: influence of social familiarity

Leyla Erden, BSc, Kathy He, BSc, Candace Burke, PhD, Paul B.S. Clarke, PhD Department of Pharmacology and Therapeutics, McGill University, Montreal QC, Canada

Introduction: Tobacco addiction is driven in part by the emergence of negative affective symptoms attributable to nicotine withdrawal. In rat preclinical models, affective processes can be investigated in terms of ultrasonic vocalization (USV) emission. While 22-kHz and 50-kHz USVs have been classically associated with negative and positive affect, respectively, this idea has proven simplistic. In fact, 50-kHz USVs comprise more than a dozen subtypes. Within this broad repertoire, evidence suggests that trill and flat call subtypes reflect positive and negative affect, respectively.

Methods: Male Long-Evans rats received nicotine in their drinking water (0, 0.05, or 0.1 mg/ml) for 3 weeks. USVs were recorded at the end of chronic exposure, and on the first two days after discontinuation. During testing, rats were paired with a familiar or unfamiliar conspecific, to assess the impact of social context on USV emission during nicotine exposure or withdrawal.

Results: Overall, unfamiliar pairs exhibited a higher prevalence of trills at the expense of flat calls, compared to familiar pairs. Nicotine withdrawal signs were dose-specific. Withdrawal from the lower dose of nicotine left flat calls unaffected while significantly reducing trills, but only in the unfamiliar pairs. This effect was transient, present at 24 hours but not 48 hours post-nicotine. Withdrawal from the higher dose of nicotine did not impact these USV measures.

Conclusions: These USV-based findings suggest that (1) rats experience positive affect when they are tested with a novel partner rather than a familiar one, and (2) rats undergoing nicotine withdrawal experience negative affect. Social context modulated affect-related vocalizations and influenced the detection of withdrawal-induced affective changes. Hence, ultrasonic vocalizations appear to provide a novel measure of affective shifts during nicotine withdrawal, which are best revealed by testing rats with an unfamiliar partner.

18. Cost-Analysis of Pharmacogenetic Testing Implementation in Depression Treatment: A Systematic Review

Rheina Firdiawati(a,b), Zhang J.(a,b), Pereira C.F. (b,c), Youssef M. (a,b), Levy-Ajzenkopf J. (b), Migas J. (a,b), Lebon I. (a,d), Persaud D. (a,b), Adamo A. (a,e), Tafazzoli D. (a,f), Mueller D. (a-c,g-h) & Kloiber S. (a-c,g). a) Department of Pharmacology and Toxicology, University of Toronto, Toronto, Canada b) Centre for Addiction and Mental Health, Toronto, Canada c) Institute of Medical Science, University of Toronto, Toronto, Canada d) Medical and Related Sciences Discovery District, Toronto, Canada e) Sunnybrook Health Sciences Centre, Toronto, Canada f) Mount Sinai Hospital, Toronto, Canada g) Department of Psychiatry, University of Toronto, Toronto, Canada h) Ontario Shores Centre for Mental Health Sciences, Whitby, Canada

Introduction: Major Depressive Disorder (MDD) is a leading cause of disability worldwide and imposes a substantial economic burden on both individuals and our healthcare systems. Although pharmacogenetic (PGx) testing has not yet been implemented into routine clinical care, it has emerged as a tool for informing pharmacotherapy decisions in MDD. Clinical trials of PGx-guided antidepressant treatment demonstrated that individuals are more likely to achieve symptom remission and experience reduced adverse drug effects compared to treatment-as-usual (TAU). The purpose of this review was to evaluate current evidence on the cost-effectiveness of PGx-guided MDD treatment and its financial impacts on the individual and healthcare system levels.

Methods: We conducted a systematic search in PubMed and Web of Science databases to identify primary studies that reported cost-analyses of PGx testing in treatment of MDD. Articles underwent screening to determine eligibility, followed by data extraction and synthesis.

Results: The search identified 18 eligible studies evaluating the economic impact of PGx-guided antidepressant treatment compared to TAU, including analyses of healthcare costs (n=5), per-member savings (n=5), cost-utility using quality-adjusted life years (QALYs; n=13), and cost-effectiveness using incremental cost-effectiveness ratios (ICERs; n=10). Findings report increased savings per member, reduced costs per QALY, and decreased ICER among

individuals receiving PGx-guided care compared to TAU. However, cost-benefit estimates varied depending on factors such as initial testing costs, whether prescribing was congruent, and symptom severity, with higher savings in individuals with moderate-to-severe MDD.

Conclusion: This review provides an evaluation of the current literature on cost savings associated with PGx-guided pharmacotherapy in MDD. Overall, the findings indicate greater cost-effectiveness compared to TAU. Variability across study designs, economic models, and healthcare systems across countries highlights the need for further research, including meta-analyses to establish improved knowledge on economic utility and to inform clinical implementation.

19. Studies of Reinforcement by Drugs of Abuse

Brooke Ginson, MSc and Francesco Leri, PhD Department of Psychology, University of Toronto Scarborough, Toronto, Ontario

Introduction: The fact that certain chemical compounds are self-administered by both humans and animals indicates that they possess reinforcing properties. However, reinforcement is not a unitary process; rather, it comprises several independent functions (White 1996). More specifically, reinforcers: 1. elicit skeletal reflexive responses; 2. activate central motivational states (Bindra 1968); and 3. promote the stabilization of recently acquired memories (White and Milner 1992), thereby increasing the likelihood that these memories will influence future behaviour.

Methods: Enhancement of memory consolidation (Gold and McGaugh, 1975; Huston and Oitzl, 1989) is considered critical to all reinforcing stimuli (White and Milner 1992) and, in fact, many drugs of abuse (e.g., alcohol, nicotine, cocaine, heroin) have memory-enhancing properties as demonstrated experimentally by the “post-training” administration method (Leri et al 2013).

Results: However, our studies in rats of the memory-enhancing function of cocaine and heroin revealed that post-training administration of these drugs does not limit their action to the consolidation of labile memories. Rather, our findings indicated that drugs administered post-training retain the ability to activate central motivational states and trigger associative learning processes (Ginson and Leri 2026; Cloke et al 2014; Rkieh et al 2014). Consequently, the behaviour of drug-exposed subjects reflects not only the influence of consolidated memories, but also the activation of qualitatively distinct yet interacting conditioned motivational states.

Conclusion: These findings have important implications for the theoretical and neurobiological understanding of how learning and memory processes contribute to the development and persistence of the addiction cycle (Koob and Volkow, 2010).

20. Greater SV2A Distribution Volume in Cortico-Striatal-Thalamo-Cortical Circuitry of Obsessive Compulsive Disorder and Relationship to Symptom Severity

Lauren R. Gray, Yuhan Karida Liu, Lucas Narcisco, Jennifer Rabin, Thomas Chao, Kimberly Desmond, Laura Miler, Alexandra Nelson, Devina Persaud, Emily Ganzorig, Erica Vieira, Stefan Kloiber, Jerry Warsh, Wei Wang, Jeffrey H. Meyer.

Introduction: Obsessive compulsive disorder (OCD) affects over 2% of adolescents and adults, approximately 35% of whom inadequately respond to treatment, so novel therapeutics are needed. To create new treatments, new targetable pathological processes need to be identified. The aims of the present study are to compare SV2A VT, a positron emission tomography (PET) marker of presynaptic density, in CSTC (caudate, orbitofrontal cortex, ventral striatum, dorsal putamen, thalamus and anterior cingulate cortex) between OCD and health, and to assess the relationship between overall OCD severity and CSTC SV2A VT. We hypothesize that SV2A VT will be greater in individuals with OCD compared to healthy controls, and that greater SV2A VT will be associated with greater severity of OCD symptoms.

Methods: [18F]SynVesT-1 PET was applied in 15 participants with OCD and 15 age- and sex-matched controls. All participants were free of psychotropic medication. Symptoms were assessed using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and the State Trait Anxiety Inventory (STAI).

Results: SV2A VT was elevated in OCD as compared to controls in all a priori regions (~15%, $F_{1,27} = 8.10$, $p<0.001$). In participants with OCD, greater SV2A VT in the CSTC was associated with greater OCD severity. State anxiety was associated with SV2A VT in the CSTC and the amygdala.

Conclusions: Greater SV2A VT is strong evidence of increased presynaptic density in the CSTC in OCD. Given the positive correlation of SV2A VT in the CSTC with greater symptom severity, and that the induction of increased presynaptic density in CSTC regions leads to repetitive behaviours in some animal models, this suggests that greater presynaptic density in the CSTC in OCD is also pathological.

21. 7T MRS Reveals Independent Associations of dACC Glutamate and GABA with Negative Symptoms in First-Episode Psychosis, Independent of Cannabis Use

Rami Hamati[1], Peter Jeon[1,2], Kesavi Kanagasabi[1], Michael Mackinley[1], Jean Theberge[3] Reggie Taylor[4], Jibran Khokhar[1], Lena Palaniyappan[1,5] [1]: Department of Anatomy and Cell Biology, Western University, London, Ontario, Canada [2]: Department of Radiology, Boston Children's Hospital, Boston, MA, USA [3]: Medical Biophysics and Psychiatry, Western University, London, Ontario, Canada [4]: University of Ottawa Institute of Mental Health Research, Ottawa, Ontario, Canada [5]: Department of Psychiatry, McGill University, Montreal, Quebec, Canada
Introduction: Glutamate and GABA, the primary excitatory and inhibitory neurotransmitters, are altered in individuals with first-episode psychosis (FEP). However, how cannabis use interacts with glutamate and GABA levels to affect symptoms remains unclear.

Methods: Using an sLASER 7T magnetic resonance spectroscopy (MRS) sequence (TR = 7500 ms, TE = 100 ms, number of averages = 32), we measured tissue fraction corrected glutamate and GABA molality (mmol/kg) in the dorsal anterior cingulate cortex (dACC) of 36 controls and 59 FEP (N = 95). In the FEP group, symptomatology was assessed using the positive and negative syndrome scale (PANSS-8) and self-reported cannabis use was assessed using the cannabis abuse screening test (CAST). MRS data was analysed using FSL-MRS; GABA data with a %CRLB > 40 were excluded. Group differences were evaluated using two-sample t-tests. Within the FEP group, separate robust regressions were used to test the interaction between cannabis use and each neurotransmitter, as well as their main effects, on symptom severity.

Results: No significant differences in glutamate (two-sample t-test; t(93) = 0.97, p = 0.33) or GABA (two-sample t-test; t(80) = -1.24, p = 0.22) were found between groups. Within the FEP cohort, there were no significant interactions between cannabis use and neurotransmitter levels on symptomatology (all p's > 0.05). However, separate main effect models controlling for age, sex and cannabis use revealed that higher dACC glutamate and GABA levels (Glutamate: B = 0.17, p = 0.03, n = 56; GABA: B = 0.83, p = 0.02, n = 47) were each associated with greater negative symptoms.

Conclusion: Altogether, these results suggest that self-reported cannabis use does not alter dACC glutamate or GABA levels to affect symptomatology. Instead, independent elevations of each neurotransmitter contribute to negative symptoms. Future studies should employ other measures of cannabis use to validate these findings.

22. Brain Fatty Acid Amide Hydrolase Levels and Trait Anxiety in Obsessive-Compulsive Disorder: Preliminary Results from a Positron Emission Tomography (PET) Study with [11C]CURB

Hanan Idd, HBSc [1,2],Gwyneth Zai, MD, PhD [1,3,4],6, Ishrat Husain, MBBS, MD [1,3,4], Richard Bazinet, PhD [5], Rachel F Tyndale, PhD [3,4],6, Isabelle Boileau, PhD [1,2,3,4], Jamie Feusner, MD [1,2,3,4],7, Stefan Kloiber, MD [1,2,3,4],6 ([1]) Institute of Medical Science, University of Toronto, Toronto, ON, Canada. [2]) Brain Health Imaging Centre, Centre for Addiction and Mental Health, Toronto, ON, Canada. ([3]) Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada. ([4]) Department of Psychiatry, University of Toronto, Toronto, ON, Canada. ([5]) Department of Nutritional Sciences, University of Toronto, Toronto, ON, Canada. (6) Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada. (7) Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

Introduction: Research on trait anxiety, characterized by an overestimation of threat, suggests a high risk of developing obsessive-compulsive disorder (OCD). Inhibition of fatty acid amide hydrolase (FAAH), a key enzyme of the endocannabinoid system (ECS), has been shown to reduce anxiety- and compulsive-like behaviours in rodent models. In this exploratory analysis, we used positron emission tomography (PET) imaging and the radiotracer, [11C]CURB to determine the relationship between FAAH levels and trait anxiety in OCD. We hypothesize that brain FAAH levels ([11C]CURB binding) will positively correlate with trait anxiety scores in individuals with OCD.

Methods: Participants with OCD completed a PET scan with the [11C]CURB radiotracer. Blood samples were collected to determine FAAH C385A rs324420 genotype. Trait anxiety was measured using the state-trait anxiety inventory (STAI) scale. Spearman's partial correlations assessed the relationship between [11C]CURB binding and trait anxiety, controlling for FAAH genotype.

Results: Trait anxiety data was available from nine individuals with OCD (M/F: 4/5; mean age: 28.78 ± 7.34). FAAH C385A genotype distribution (OCD: C/C(N=6), A/C(N=3) was significantly associated with [11C]CURB binding. Correlation analyses revealed a significant negative correlation between trait anxiety and [11C]CURB binding in the whole brain (r=-0.737, p=0.037) and in prefrontal, temporal, occipital, parietal, insular cortices, dorsal and ventral striatum, hippocampus, and thalamus (-0.626 < r < -0.737; 0.097 < p < 0.037). A marginally significant negative correlation was observed in the amygdala (r=-0.683, p=0.062).

Conclusion: These preliminary findings suggest that lower FAAH levels are associated with higher trait anxiety in individuals with OCD. This may reflect altered ECS signalling in OCD, although analyses of a larger sample, and transdiagnostically, are important to determine this more definitively and to understand the specificity.

23. Polygenic Risk for Cardiovascular Risk Factors and Suicide Risk Behaviors among Youth with and at Risk for Bipolar Disorder

Simin Jin, BSc, Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, ON, Canada; Department of Pharmacology, University of Toronto, Toronto, ON, Canada; Mikaela K. Dimick, PhD, Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, ON, Canada; Kody G. Kennedy, PhD, Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, ON, Canada; Clement Zai, PhD, Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, ON, Canada; Department of Psychiatry, University of Toronto, Toronto, ON, Canada; Benjamin I. Goldstein, MD PhD, 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

Introduction: Cardiovascular risk factors (CVRFs) are associated with elevated risk of suicide attempt in bipolar disorder; however, little is known about whether this risk is driven by genetic risk for CVRFs. We therefore examined CVRF polygenic risk scores (PRSs) in relation to suicide risk behaviors [i.e., suicide attempt and non-suicidal self-injury (NSSI)] in youth with and at risk for BD, hypothesizing that higher CVRF-PRSs are associated with suicide attempt.

Methods: Participants were 273 youth, ages 13-20, with BD (n=161) and at risk for BD (n=112), including 62 with a lifetime history of suicide attempt, 114 with NSSI alone, and 97 without suicide attempt or NSSI. PRSs for hypertension, body mass index (BMI), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and type 2 diabetes were computed using summary statistics from adult genome-wide association studies. Multinomial logistic regression examined the association of CVRF-PRSs with suicide risk behaviors in the overall sample and within diagnostic subgroups, controlling for age, sex, and the first two genetic principal components.

Results: CVRF-PRSs were not associated with suicide attempt or NSSI in the overall sample. In youth with BD, higher hypertension-PRS was associated with suicide attempt (OR=1.67 [1.01, 2.76], p=0.04), but did not survive correction for multiple comparisons. In youth at risk for BD, higher BMI-PRS was associated with suicide attempt (OR=2.64 [1.36, 5.15], p=0.004).
Conclusion: This study provides preliminary evidence linking CVRF-PRSs with suicide attempt in youth with and at risk for BD, suggesting their potential value in suicide risk prediction. Future studies are warranted to evaluate the mediating effects of CVRFs and explore differences across diagnoses.

24. Single-Shot GABA-Selective Spectroscopy via DANTE-PRESS at 7T: an in vivo proof-of-concept (Submitted and accepted but not presented)

Kesavi Kanagasabai[1,2,3], Omer Oran[4], Lena Palaniyappan[1,2,3],6, Jean Théberge[1,2,5] Affiliations: [1]. Imaging Program, Lawson Research Institute , [2]68 Grosvenor Street, N6A[4]V[2] London, ON, Canada. [2]. Department of Medical Biophysics, Western University,

London, ON, Canada. [3]. Robarts Research Institute, Western University, London, Ontario, Canada. [4]. Siemens Healthcare Limited, Oakville, Ontario, Canada [5]. Department of Medical Imaging, St. Joseph's Health Care London, [2]68 Grosvenor Street, N6A[4]V[2] London, ON, Canada. 6. Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Montréal, Québec, Canada.

Introduction: Metabolite-selective proton magnetic resonance spectroscopy (1H-MRS) techniques are often used to isolate low concentration metabolites such as gamma-amino butyric acid (GABA). However, GABA multiplets overlap with macromolecules and neighbour abundant metabolites. Furthermore, most metabolite-selective techniques involve spectral editing that may introduce subtraction-related artifacts. Using a single-shot frequency-selective sequence known as Delays-Alternating-Nutation-Tailored-Excitation-Point-RESolved-Spectroscopy (DANTE-PRESS), we present results on its precision when measuring GABA at 7 Tesla in phantoms and human brain as an in vivo proof-of-concept.

Methods: DANTE-PRESS was programmed within the software environment of the Siemens Magnetom 7 Tesla MR scanner at the Centre for Functional Metabolic Mapping at Robarts Research Institute at Western University. Test-retest scans were obtained on phantoms, 3 healthy volunteers (20x20x20mm3 voxel at the dorsal anterior cingulate cortex) as an in vivo proof-of-concept, and 10 healthy controls to isolate GABA.

Results: Qualitatively, DANTE-PRESS was able isolate GABA while reducing contributions from co-refocused metabolites and suppressing all signal outside of its passband in phantoms and in vivo. In vivo, the inter-individual coefficients of variance of GABA was less than 13.53% and the mean Cramer-Rao Lower Bounds of GABA was 10.14 %.

Conclusion: Double DANTE-PRESS can effectively isolate GABA, a low concentration metabolite, thereby simplifying spectral quantification allowing for precise measurements. Future work includes acquiring GABA, glutamate, and glutathione within a single session to assess the excitation and inhibition imbalances along with the role of oxidative stress in patients with neurocognitive disorders.

25. Generalization of opioid agonists to morphine-elicited stimulus effects in rats trained on appetitive and inhibitory learning contingencies.

Jessica M. Karlovcec, MSc [1,2], Ella V. Claridge, BSc [1,2], Jiayu Zheng, BSc [1,2], Davin R. Peart MSc [1,2], Adiia P. Stone BSc [1,2], Jennifer E. Murray, PhD [1,2]. [1] Department of Psychology, University of Guelph, Guelph, ON, Canada [2] Collaborative Neurosciences Graduate Program, University of Guelph, Guelph, ON, Canada

Introduction: Interoceptive effects elicited by opioids can guide behaviours through Pavlovian associations with drug-related stimuli; thus, following acquisition of appropriate conditioned sucrose-seeking guided by a morphine stimulus, stimulus specificity can be determined by comparing behaviour elicited by different opioid receptor agonists to baseline discrimination behaviour. This study aimed to determine if and at which doses of oxycodone, fentanyl, and hydromorphone generalize to a training dose of morphine in male and female rats, with the hypothesis that dose-dependent generalization of these drugs to the training dose of morphine would be found.

Methods: Male and female rats received daily injections of either morphine or saline before training sessions, which consisted of 8 presentations of a white noise (WN) conditioned stimulus. WN was followed by sucrose delivery on morphine, but not on intermixed saline sessions for rats trained on a feature positive (FP) learning contingency. The opposite was true for rats trained on a feature negative (FN) contingency. After at least 32 training sessions and the acquisition of stable discrimination, rats completed generalization cycles with two qualification sessions identical to training, followed by a test session if a minimum discrimination between qualification sessions was demonstrated. On tests, responding to a single WN presentation was recorded after pre-treatment with one of four doses of either morphine, oxycodone, hydromorphone, fentanyl, naloxone co-administered with morphine, or saline. All rats were tested on all drugs.

Results: All rats acquired the discrimination. Oxycodone, fentanyl, and hydromorphone generalized to the training dose of morphine dependent upon dose and learning history. Naloxone attenuation of agonist-appropriate responding was clear only in FP rats.

Conclusions: Our findings demonstrate that the stimulus effects elicited by morphine can generalize to other opioid agonists, and morphine-conditioned responding is mediated by mu opioid receptors in FP-trained rats, as indicated by blockade of this responding by naloxone.

26. Effects of Sex, Treatment Resistant Depression, and Antidepressant Treatment on Monoamine Oxidase B Total Distribution Volume

Emily J.Y. Kuik, BSc;[1,2,3] Catalina Baena-Tan;[1,2] Sho Moriguchi, MD, PhD;[4,5] Joeffre Braga, PhD;[1,2] Laura Miler, HBSc;[1,2] Pablo Rusjan, PhD;6,7 Michael Bagby, PhD; 8,9,[1]0 M. Ishrat Husain, MD, PhD;8,[11] Stefan Kloiber, MD, PhD;8,[12] Neil Vasdev, PhD;[1,2] and Jeffrey H. Meyer, MD, PhD, FRCPC[1,2,3],8 Affiliations: [1] Brain Health Imaging Centre, Centre for Addiction and Mental Health, Toronto, ON, Canada [2] Azrieli Centre for Neuro-Radiochemistry, The Centre for Addiction and Mental Health, Toronto, ON, Canada [3] Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada [4] Department of Functional Brain Imaging Research, National Institute of Radiological Sciences, National Institutes for Quantum and Radiological Science and Technology, Chiba, Japan [5] Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan 6 Douglas Research Centre, McGill University, Montreal, QC, Canada 7 Department of Psychiatry, McGill University, Montreal, QC, Canada 8 Department of Psychiatry, University of Toronto, Toronto, ON, Canada 9 Department of Psychology, University of Toronto, Toronto, ON, Canada [1]0 Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada [11] Clinical Trials Unit, Centre for Addiction and Mental Health, Toronto, ON, Canada [12] General Adult Psychiatry and Health Systems Division, Centre for Addiction and Mental Health, Toronto, ON, Canada

Introduction: Monoamine oxidase B (MAO-B) is a high-density protein that influences mitochondrial function and the transition to astrogliosis, and produces hydrogen peroxide while metabolizing non-serotonergic monoamines; its level is elevated in several common neuropsychiatric diseases, including the prefrontal cortex (PFC) of major depressive episodes (MDE), and the cortex of persistent traumatic brain injury, long COVID, and Alzheimer's disease. The aims of the present study are to examine the effect of sex, treatment-resistant depression, and antidepressant treatment on MAO-B total distribution volume ([11C]SL25.1188 VT), an index of MAO-B level, and we hypothesize that [11C]SL25.1188 VT will be lower in females compared to males; elevated in individuals with MDE and a history of treatment-resistance

(TRD) compared to individuals with MDE and no history of treatment-resistance (NTR-MDE); and lowered after treatment with rasagiline or phenelzine but not duloxetine.

Methods: [11C]SL25.1188 PET was applied in 95 participants (29 with NTR-MDE, 26 with TRD, and 40 healthy). A subset of NTR-MDE and TRD were scanned before and after treatment (administered orally once daily for 4-6 weeks) to determine the effects of phenelzine, rasagiline, and duloxetine.

Results: [11C]SL25.1188 VT was significantly higher in females compared to males (13.3%, F1,91 = 16.263,?p?<.001) in prioritized grey matter regions (including PFC, anterior cingulate cortex, and hippocampus), and in TRD compared to NTR-MDE in the PFC (6.0%, F1,52 = 4.78,?p?= .033). Occupancy of rasagiline and phenelzine was approximately 94%, but duloxetine had negligible effects.

Conclusions: These findings raise important implications, including whether sex differences in MAO-B level may contribute to sex differences in the prevalence or course of diseases associated with elevated MAO-B levels; consideration of targeting MAO-B in some TRD states; and whether rasagiline should be assessed in clinical trials for use beyond Parkinson's disease, given its comparably high MAO-B occupancy to phenelzine.

27. Treatment with Psilocybin for Chronic Neuropathic Pain and Depression

Jordana Kazdan, BA ([1,2]), Karim Ladha, MD, MSc, FRCPC ([3]), Venkat Bhat, MD, MSc, FRCPC, DABPN ([4]), Daniel Blumberger, MD, MSc, FRCPC ([1,4]), Hance Clarke, MD, FRCPC, PhD ([3]), Akash Goel, MD, MPH, FRCPC ([3]), Brett Jones, MD, PhD ([1,4]), Tyler Kaster, MD, PhD ([1,4]), Joel Katz, PhD ([5]), Paul Ritvo, PhD ([5]), Daphne Voineskos, PhD ([4]), Wei Wang, PhD ([1]) , Duminda Wijeysundera, MD, PhD, FRCPC ([3]), Ishrat Husain, MBBS, MD(Res.), FRCPsych (UK), FRCPC ([1,2,4]) ([1]) Temerty Center for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, Toronto, ON, Canada ([2]) Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada ([3]) Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto, ON, Canada([4]) Department of Psychiatry, University of Toronto, Toronto, ON, Canada ([5]) Department of Psychology, York University, Toronto, ON, Canada

Introduction: Psilocybin therapy has re-emerged as a promising intervention for treatment-resistant depression (TRD) and preliminary evidence supports the potential of psilocybin to alleviate symptoms of neuropathic pain. Despite the high prevalence of neuropathic pain and TRD, there is limited clinical evidence investigating psilocybin therapy for this comorbidity. To address this gap, this pilot clinical trial aims to 1) determine the feasibility and safety of one oral dose of psilocybin (25 mg) combined with psychological support in adults with comorbid chronic neuropathic pain and TRD, and 2) provide preliminary evidence on whether psilocybin therapy can improve pain and depression symptom severity from baseline to 1-week post-treatment.

Methods: This is a proof-of-concept, open-label trial administering psilocybin therapy in 16 adults with comorbid chronic neuropathic pain and TRD (NCT06518720). We will assess whether three key feasibility metrics are attainable: recruitment (> 20% of eligible patients), adherence (>90%) and minimal loss to follow-up (<10%). Safety outcomes include frequency and severity of adverse events throughout the 3-month follow-up period. Clinical outcomes include pain intensity and interference as determined by Patient Reported Outcomes Measurement Information System (PROMIS) questionnaires, and depressive symptoms as

determined by the Montgomery–Åsberg Depression Rating Scale (MADRS) assessed at baseline and at days 1, 7, 14, 30, and 90 post psilocybin treatment. Given the pilot nature of this study, clinical outcomes will be analyzed on an intention-to-treat basis and summarized descriptively.

Results: This trial is ongoing (n=3 enrolled to date). Analyses presented will reflect early-stage data prior to study completion. Findings will focus on feasibility and safety outcomes, including recruitment processes, protocol adherence, and adverse event reporting.

Conclusion: Determining the feasibility and safety of psilocybin therapy in a clinical trial setting can inform study design, dosing procedures, and a sample size required to observe treatment-related effects in future larger-scale trials.

28. Access to Child Psychiatry in Three Settings: A Personal Reflection

Tigist Kebede

Introduction: Child and adolescent mental health (CAMH) is shaped not only by biology and development but also by the cultural, ancestral, and communal worlds in which children grow. This reflection draws on my clinical experiences across rural and urban Ethiopia, Cape Town, and Toronto to show how culturally grounded systems of care shape psychiatric practice. In Ethiopia, limited formal services and resource scarcity highlight the central role of extended family networks and traditional healing. Psychiatry often extends beyond clinic walls as clinicians collaborate with families who rely on herbal medicine and spiritual care. These practices reinforce belonging and identity, showing that healing is relational and collective rather than solely biomedical.

Methods: Competencies such as recognizing personal biases, communicating across cultural differences, and adapting assessment and treatment to each family's context are essential. In Cape Town, CAMH sits between the advanced medical systems of Toronto and the resource limitations of Ethiopia. In one province, I observed well developed multidisciplinary teams and strong community psychiatry; in another, access to CAMH was extremely limited. Care is deeply intertwined with ancestry and cultural rituals such as Imbeleko. High rates of trauma make trauma informed care indispensable, yet cultural rituals and extended kinship systems also play a powerful positive role. Toronto represents a high resource, specialized system where precision medicine and evidence based interventions are standard, though timely access remains a topic of discussion. Its multicultural population requires clinicians to integrate bicultural identities and diverse explanatory models into care. Indigenous healing practices, such as smudging, show how traditional rituals can complement CAMH.

Results: Across all three settings, gaps in CAMH access persist, though the causes and expressions differ.

Conclusion: In summary, culturally grounded psychiatry is a foundational element not an optional enhancement that improves access to care and shapes assessment and treatment to align with a child's cultural values and lived experiences.

29. Amygdala Reactivity to Emotional Faces and FAAH Levels Assessed by fMRI and PET in Social Anxiety Disorder

Martin Kronenbuerger, MD, PhD[12]; Christina F. Pereira, PhD candidate[12]; Miray Youssef, PhD candidate[12], Thomas Tan[123]; Rheina Firdiawati, PhD candidate[14]; Maria T. Secara, PhD candidate[14]; Pablo M. Rusjan, PhD[5]; Rachel F. Tyndale, PhD[134]; M. Ishrat Husain, MD[123]; Jerry Warsh, MD[123]; Bernard Le Foll, MD, PhD[1234]6; Gwyneth Zai, MD, PhD[1234]; Colin Hawco, PhD[123]; Isabelle Boileau, PhD[1234]; Stefan Kloiber, MD[1234] [1] Centre for Addiction and Mental Health, Toronto, ON, Canada [2] Institute of Medical Science, University of Toronto, Toronto, ON, Canada [3] Department of Psychiatry, University of Toronto, Toronto, ON, Canada [4] Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada [5] Department of Psychiatry, McGill University, Montreal, QC, Canada 6 Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada

Introduction: Endocannabinoid signaling in corticolimbic circuits plays an important role in stress regulation, anxiety and social behaviour. Levels of fatty acid amide hydrolase (FAAH), a key regulator enzyme of endocannabinoid signaling, can be measured using positron emission tomography (PET). This study evaluates corticolimbic signaling in individuals with Social Anxiety Disorder (SAD) and healthy controls (HC) using functional magnetic resonance imaging (fMRI) and its association with PET-derived FAAH levels. Positive FAAH–amygdala associations were previously reported in HC, but remain unclear in SAD.

Methods: 16 individuals with SAD (25.2±5.6 years) and 20 HC (24.3±4.6 years) completed fMRI using a Hariri paradigm (emotional faces>shapes) to assess amygdala reactivity. Whole-brain analyses using non-parametric permutation testing and mean values were extracted from amygdala regions of interest (ROI). FAAH levels in the amygdala were assessed by PET [^{11}C]CURB binding (?k3 as an index of FAAH levels). FAAH genotyping was performed. Clinical symptoms were assessed by the Liebowitz Social Anxiety Scale (LSAS). Linear regression assessed associations between amygdala reactivity, FAAH levels, and clinical scores before and after genotype adjustment.

Results: Whole-brain activation maps (N = 36) showed occipital and bilateral amygdala activation. Mean amygdala ROI activation did not differ between SAD and HC (all $p > 0.05$). FAAH genotype distribution did not differ between groups (?^{2}(2)=2.20, p=0.3). In SAD, higher FAAH levels were associated with lower right amygdala fMRI activation (ß=-0.60, p=0.02). No significant association was observed in HC (ß=-0.13, p=0.5). In the comparison of SAD vs HC, a significant group×FAAH level interaction for right amygdala activation (ß=2.47, p=0.04) was reduced to trend-level after adjustment for FAAH genotype (ß=2.51, p=0.09). LSAS scores were not associated with amygdala fMRI activation.

Conclusions: Analysis suggests that higher FAAH levels were associated with lower amygdala reactivity in SAD, contrasting with prior findings in HC. Further research is needed to confirm findings.

30. Neurocognitive Functioning in Social Anxiety Disorder and Its Associations with Corticolimbic Circuitry and Endocannabinoid System Function

Martin Kronenbuerger, MD, PhD[12]; Christina F. Pereira, PhD candidate[12]; Miray Youssef, PhD candidate[12]; Thomas Tan, PhD[125]; Rheina Firdiawati, PhD candidate[13]; Pablo M. Rusjan, PhD6; Rachel F. Tyndale, PhD[135]; M. Ishrat Husain, MD[125]; Jerry Warsh, MD[125]; Bernard Le Foll, MD,

PhD[1235]7; Gwyneth Zai, MD, PhD[1235]; Colin Hawco, PhD[125]; Isabelle Boileau, MD[1235]; Stefan Kloiber, MD[1235] Affiliations [1] Centre for Addiction and Mental Health, Toronto, Ontario, Canada [2] Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada [3] Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada [4] Translational Addiction Research Laboratory, Toronto, Ontario, Canada [5] Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada 6 Department of Psychiatry, McGill University, Montreal, Quebec, Canada 7 Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada

Introduction: Social anxiety disorder (SAD) is characterized by persistent fear and anxiety in social settings and may be associated with subtle neurocognitive deficits. Altered endocannabinoid signaling has been implicated in the regulation of stress and anxiety. Levels of fatty acid amide hydrolase (FAAH), a key regulator of this system, can be measured using [^{11}C]CURB positron emission tomography (PET). This study aimed to examine neurocognitive functioning in individuals with SAD and healthy controls (HC) and its association with corticolimbic activity measured by functional magnetic resonance imaging (fMRI) and FAAH levels measured by PET.

Methods: Forty-one individuals with SAD (26.4±5.7 years) and 25 HC (24.8±4.6 years) were assessed. The Trail Making Test (processing speed, cognitive flexibility), Digit Span (working memory), Hopkins Verbal Learning Test–Revised (verbal learning), Delay Discounting Task (impulsivity, decision-making), Grooved Pegboard Test (motor speed), Continuous Performance Test (sustained attention), and Stop-Signal Task (response inhibition) were administered. Participants completed fMRI using an emotional faces paradigm to assess amygdala reactivity with region of interest (ROI) extraction. FAAH levels were measured using [^{11}C]CURB PET across 11 ROIs. Clinical symptoms were assessed using the Liebowitz Social Anxiety Scale and the Depression Anxiety Stress Scales. Group differences were assessed using t-tests, and linear regression analyses examined associations between neurocognitive performance, imaging, and clinical scores, controlling for FAAH genotype.

Results: Individuals with SAD showed lower working memory performance compared to HC on the Digit Span Backward test (SAD: 6.68±1.89; HC: 8.04±2.26; $p = 0.011$), with no group differences in other neurocognitive measures (all $p > 0.05$). Neurocognitive performance was not associated with fMRI activation, FAAH levels, or clinical measures (all $p > 0.05$).

Conclusion: In this exploratory analysis, subtle working memory deficits in SAD were identified but no associations with imaging measures or clinical symptom severity were detected. The underlying mechanisms and clinical relevance require further investigation.

31. Higher Mitochondrial Polygenic Risk Scores Are Associated with Lower Cerebral Blood Flow in Youth with Bipolar Disorder

Nidhi P. Kulkarni, PhDa, Clement C. Zai, PhD, MPHb,c, Kody G. Kennedy, PhDa, Megan Mio, PhDa, Ana C. Andreazza, PhDb,c,d, Vanessa F. Goncalves, PhDb,c, L. Trevor Young, MD, PhDb,c,d, Bradley J. MacIntosh, PhDe,f,g,h, Benjamin I. Goldstein, MD, PhDa,c,d aCentre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, ON, Canada bCentre for Addiction and Mental Health, Toronto, ON, Canada cDepartment of Psychiatry, University of Toronto, Toronto, ON, Canada dDepartment of Pharmacology & Toxicology, University of Toronto, Toronto, ON, Canada eComputational Radiology & Artificial Intelligence Unit, Department of Physics and Computational Radiology, Oslo University Hospital, Oslo, Norway

fSandra E Black Centre for Brain Resilience and Recovery, Sunnybrook Research Institute, Toronto, ON Canada gDepartment of Medical Biophysics, University of Toronto, Toronto, ON, Canada hHurvitz Brain Sciences Program, Sunnybrook Research Institute, Toronto, ON, Canada

Introduction: Bipolar disorder (BD) is a polygenic disease characterized by mitochondrial dysfunction and anomalous cerebral blood flow (CBF), which are interconnected. We examined the association of mitochondrial polygenic risk scores (Mito-PRS) with CBF in relation to youth BD.

Methods: 100 participants (17.1±1.6 years old; n=61 BD, n=39 controls) underwent arterial spin labelling magnetic resonance imaging to quantify CBF. Mito-PRS was derived from a subset of variants within BD-PRS and were selected based on their location within genes annotated in expertly curated mitochondrial gene databases. Covariate-adjusted analyses examined the association of Mito-PRS with CBF in global grey matter, and anterior cingulate cortex and amygdala regions of interest. Sex-stratified analyses and PRS-by-diagnosis interaction effects were also examined. Sensitivity analyses controlled for psychotropic medications, traditional cardiovascular risk factors, and mood.

Results: Higher Mito-PRS was associated with lower global grey matter CBF in the overall sample (ß=-0.29, p=0.003) and within BD (ß=-0.36, p=0.006). These findings were significant in females but not males. Following sensitivity analyses, most findings remained significant and additional findings emerged. Specifically, Mito-PRS associations with regions of interest were not significant in primary analyses but were significant when controlling for cardiovascular risk factors and mood.

Conclusion: In a sample of youth with BD, higher Mito-PRS was associated with lower global CBF, particularly in females. Controlling for cardiovascular risk factors and mood strengthened study findings. Future studies powered to evaluate cardiovascular risk-related effects, mood-related effects, and putative mediators of the observed findings are warranted.

32. The Transition to Psychopathology: Repeat mGluR5 PET Scans in High-Risk Volunteers

Maja Nikolic; Maisha Iqbal; Nicole Palacio; Charlotte Caswell; Sylvia M.L. Cox; Jean R. Séguin; Gassan Masserweh; Frank Vitaro; Mara Brendgen; Sophie Parent; Michel Boivin; Sylvana Côté; Richard E. Tremblay; Natalie Castellanos Ryan; **Marco Leyton**

Introduction: Type 5 metabotropic glutamate receptors (mGluR5) affect experience-dependent neuroplasticity, influencing the ability to adapt to changing environments. The availability of these receptors is reported to be altered across drug- and stress-related disorders, but results have been inconsistent. To investigate these effects more thoroughly, we conducted repeat positron emission tomography (PET) scans in young adults before and after they developed a mental health disorder.

Methods: PET-[^{11}C]ABP688 scans were conducted in longitudinally followed youth at ages 18 (Wave-1, n=59) and 25 (Wave-2, n=44). Binding potential (BPND) values were derived for 11 striatal and extrastriatal regions of interest (ROIs). Linear mixed-effects models examined

effects of Group (Emerging DSM-5 Disorder vs Control), Time, and ROI. Post hoc comparisons were Bonferroni-corrected.

Results: From Wave-1 to Wave-2, some participants developed mood (n=9), anxiety (n=9), ADHD (n=3), OCD (n=1), and substance use disorders (n=6). Both healthy controls and the emerging DSM-5 disorder group showed decreases in BPND over the seven-year follow-up, but, across ROI, these declines were greater in the DSM-5 group (Group x Wave interaction, p=.007). As previously reported, tobacco smokers exhibited lower BPND values than non-smokers and this was seen in all regions (ß= -0.044, p=.004). After controlling for smoking, lower BPND values were also predicted by higher than average illicit drug use occasions (ß= -1.02×10^(-4), p=.005) and larger increases in Wave-1 to Wave-2 drug use predicted larger decreases in BPND (ß= -7.43×10^(-5), p<.001). Lower Wave-2 BPND values were also associated with higher Wave-2 stress (ß= -0.009, p<.001) and this negative association was amplified by greater increases in drug use (interaction ß= -2.97×10^(-5), p<.001).

Conclusions: This study provides the first longitudinal evidence that decreases in mGluR5 availability are associated with a wide range of mental health problems. The effects are related to stress yet, across diagnoses, are largely driven by cumulative substance use.

33. Neuroepigenetic Effects of Stress and Cocaine: PET [11C]Martinostat and Postmortem Tissue Studies of Class I HDACs

Nicole Palacio, Kaan Salcin, Maja Nikolic, Sylvia Cox, Dariusz Zurawek, Ghazal Fakhfouri, Maria Antonietta Davoli, Reza Rahimian, Rafael Maldonado, Pablo Rusjan, Naguib Mechawar, Gassan Massarweh, Gabriella Gobbi, Linda Booij, Pedro Rosa-Neto, Gustavo Turecki, Jacob Hooker, **Marco Leyton**

Introduction: The long-lasting effects of epigenetic modifications make them compelling candidate mechanisms for the enduring susceptibility to addictions provoked by early-life trauma and drug use itself. Both effects have been identified in animal models. Now, for the first time, we are able to investigate these effects in living human brain using positron emission tomography (PET).

Methods: With the novel PET tracer, [11C]Martinostat, we quantified brain regional densities of the epigenetic modifying enzymes, class I histone deacetylases (HDAC1,2,3), and complemented this with analyses of postmortem ventral striatum tissue from the NIH NeuroBioBank. PET studies were completed in 58 volunteers, including 38 cocaine users and 20 stimulant drug-naïve controls. Data were analyzed with Linear Mixed Models, ANCOVA, and correlations, using parametric and non-parametric versions as appropriate.

Results: In the white matter, [11C]Martinostat SUVR values were higher in the cocaine use disorder group vs healthy controls and recreational users (p=0.009). The higher the lifetime cocaine use, the higher the white matter [11C]Martinostat SUVR (p=0.004 in users). Stress and trauma had effects also. The higher the recent stress (p=0.01 in all participants) and early-life trauma (p=0.04 in users), the higher the [11C]Martinostat SUVR in caudate. Mediation analyses indicated that the effect of early-life trauma was driven by recent stress (ab=0.0013; SE=0.0007; 95% CI: [0.0001, 0.0031], n=36) and lifetime cocaine use (ab= -0.001, SE=0.0004, 95% CI: [-0.0019, -0.0003], n=58). Western Blot data from postmortem tissue raised the possibility that some of these increases were driven by HDAC3 (p=0.007) since HDAC3 protein levels were

higher in cocaine users with early-life trauma (n=8) compared to healthy controls (n=14; p=0.07) and cocaine users without early trauma (n=14; p=0.006).

Conclusion: Together, our findings provide the first evidence that stress, early-life trauma, and drug use can affect the neuro-epigenetics of living human brain.

34. Implementation of Pharmacogenetic Testing at Ontario Shores Centre for Mental Health Sciences

Mugeng Liu[12]; Gokulan Kandasamy[1]; Susan Wei[1]; Carman Brown[1]; Ben Rogers[1]; Philip Klassen, MD[12]; Daniel Mueller, MD, PhD[123] [1] Ontario Shores Centre for Mental Health Sciences, Whitby, ON, Canada [2] Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada [3] Centre for Addiction and Mental Health, Toronto, ON, Canada

Introduction: Pharmacogenetic research has identified several genes associated with responses to mental health medications and has established several evidence-based guidelines. However, implementation has been lagging. As the first of its kind, the Ontario Shores Centre has recently begun implementation for inpatients and outpatients as part of routine clinical care. Here, we report PGx testing results for CYP2D6 and CYP2C19 from our clinical cohort.

Methods: This implementation study was conducted beginning in September 2024. Psychiatric inpatients with severe mental illness were invited to undergo PGx testing to optimize medication treatment. Metabolism status identification followed Clinical Pharmacogenetics Implementation Consortium (CPIC) nomenclature. Descriptive analyses were used to summarize phenotype distributions.

Results: Between September 2024 and March 2026, 546 inpatients underwent PGx testing. For CYP2C19, 38.5% exhibited normal metabolizer status, while 31.5% and 21.2% were intermediate and rapid metabolizers, respectively. Poor metabolizers accounted for 4.8%, and ultrarapid metabolizers for 4.0%. For CYP2D6, 61.2% were normal metabolizers and 32.2% were intermediate metabolizers, while 3.3% and 1.1% were classified as poor and ultrarapid metabolizers, respectively. Overall, only 23.4% (n = 128) of inpatients exhibited normal metabolism for both genes, and 0.5% (n = 3) exhibited extreme metabolism for both.

Conclusion: PGx testing revealed a high prevalence of non-normal metabolizer phenotypes among inpatients with severe mental illness, which may impact medication efficacy. The observed distribution is consistent with previous reports in populations of predominantly European ancestry. These findings support the potential utility of PGx-guided prescribing in psychiatric settings and highlight the need for further studies to evaluate its impact on treatment outcomes and medication safety.

35. Loss of Vesicular Monoamine Transporter 2 in Striatum of Long COVID and Relationship to Neuropsychiatric Symptoms

Yuhan Karida Liu[1,2], Devina Persaud[1], Erica L Vieira[1], Joeffre Braga[1], Pablo Rusjan[3], Laura Miler[1], Jennifer S Rabin[1],6, [1]0, [11], Tina McCluskey[1], Isabelle Boileau[1,2,4], Thomas Chao7, Michael Bagby[4], Lucas Narciso[1,4], Lauren Rose Gray[1,2], Neil Vasdev[1], Kimberly Desmond[1,4], Stefan Kloiber[1,2,4], Jerry Warsh[1], Muhammad Ishrat Husain[1,2,4],8, Kelly Smart[1,5], Wei Wang[1],9,

Jeffrey H Meyer[1], [2], [4] [1] Brain Health Imaging Centre, Campbell Family Mental Health Research Institute, The Centre for Addiction and Mental Health, Toronto, Ontario, Canada [2] Department of Pharmacology and Toxicology, University of Toronto, Toronto, Canada [3] Department of Psychiatry, McGill University, Montreal, Quebec, Canada [4] Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada [5] Australian Nuclear Science and Technology Organisation, Sydney, New South Wales, Australia 6 Harquail Centre for Neuromodulation, Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Toronto, Ontario, Canada 7 Forward Thinking Psychological Services, Vancouver, British Columbia, Canada 8 Krembil Brain Institute, University Health Network, Toronto, Ontario, Canada 9 Department of Psychological Clinical Science, University of Toronto Scarborough, Toronto, Ontario, Canada [1]0 Division of Neurology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada [11] Rehabilitation Sciences Institute, University of Toronto, Canada

Introduction: Dopaminergic neurons are vulnerable to injury from gliosis and have high density of ACE2 receptors, but the integrity of dopaminergic neurons has not been investigated in long COVID. This study examined whether vesicular monoamine transporter 2 (VMAT2) binding, index of dopamine-releasing neuron density, is reduced in the striatum in long COVID and associated with neuropsychiatric symptoms.

Methods: This case-control study (Aug 2022-Apr 2024, Toronto, Canada) included 24 adults with long COVID and 24 age-matched healthy controls, and the healthy sample was extended to 43 for exploratory analyses. Primary outcome was comparison of (+)[¹¹C]DTBZ binding potential (BPND), PET measure of VMAT2 binding, between long COVID and control groups across ventral striatum, dorsal putamen, and dorsal caudate. Secondary outcomes were associations of regional (+)[¹¹C]DTBZ BPND with neuropsychiatric measures (apathy, anhedonia, motor retardation) in long COVID.

Results: (+)[¹¹C]DTBZ BPND was significantly lower in 24 long COVID vs 24 age-matched controls (linear mixed effects model, P=0.00004; vs 43 controls, P=0.0006). Apathy, motor slowing, and memory decline correlated with lower (+)[¹¹C]DTBZ BPND in ventral striatum, dorsal putamen and caudate, respectively (|r|= 0.48 to 0.58, P=0.0029 to 0.018). These symptoms that correlated with lower (+)[11C]DTBZ BPND also differed between Long COVID cases and healthy controls who recovered well after COVID-19. Long COVID was associated with greater symptom severity on the Marin Apathy Evaluation Scale (P<0.000001), Cognitive Failures Questionnaire (P=0.00005), Finger Tapping Test Dominant Hand (P=0.0001) and the Hopkins Verbal Learning Test–Revised Delayed Recall (P=0.00006).

Conclusion: Findings provide strong evidence for loss of dopamine releasing neurons in long COVID. Loss of dopamine nerve terminals may be contributing to symptom correlates of apathy, motor slowing and memory decline suggesting improved function of dopaminergic synapses as a new therapeutic direction to treat long COVID.

36. Semaglutide Improves Health-Related Quality of Life in Major Depressive Disorder: Evidence for Metabolic and Motivational Pathways

Cristian-Daniel Llach Lopez ([1]) Sebastian Badulescu ([1]) Aniqa Tabassum ([1]) Hiya Shah ([1]) Hartej Gill ([1]) Ryan Brudner ([1]) Riccardo de Giorgi ([2]) Eduard Vieta ([3]) Roger S. McIntyre ([1]) Joshua D. Rosenblat ([1]) Rodrigo Mansur ([1]) ([1]) Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada ([2]) Department of Psychiatry, University of Oxford, Oxford, United

Kingdom ([3]) Department of Psychiatry and Psychology, University of Barcelona, Barcelona, Catalonia, Spain

Introduction: Health-related quality of life (HRQoL) and motivation are key determinants of functional recovery in major depressive disorder (MDD) and remain insufficiently addressed by current treatments. We evaluated whether adjunctive semaglutide improves HRQoL in MDD and examined whether metabolic and motivational changes are associated with these effects.

Methods: This secondary analysis used data from a 16-week, double-blind, placebo-controlled randomized trial of adjunctive oral semaglutide in adults with MDD, cognitive dysfunction, and overweight/obesity (2022–2024). Participants continued stable antidepressant therapy. HRQoL (SF-36), depressive symptoms (HAMD-17), metabolic parameters (HbA1c, fasting glucose, HOMA2-IR), cognition, and effort-based motivation (Effort Expenditure for Rewards Task; EEfRT) were assessed from baseline to week 20. Generalized estimating equations evaluated longitudinal treatment effects, and regression and PROCESS models examined associations and indirect effects.

Results: Seventy-two participants were randomized (semaglutide n=35; placebo n=37), with 75% completing week 16. At baseline, lower HRQoL was associated with greater depressive severity, higher BMI and insulin resistance, and poorer cognition. A significant treatment-by-time interaction was observed for HRQoL (p=0.027), with greater improvement in the semaglutide group at week 16 (+11.8 vs +4.0 points; p=0.015). Effects remained after adjustment for depressive symptom changes. Improvements in HRQoL were associated with reductions in HbA1c (ß = –131.37, 95% CI –225.11 to –37.63; p=0.006) and effort discounting (ß = –1.80, 95% CI –3.49 to –0.10; p=0.038). Mediation analyses suggested a potential indirect effect via HbA1c (95% CI 0.77–11.53), and moderation analyses indicated that changes in effort discounting influenced the association between treatment and HRQoL (p=0.039).

Conclusion: Adjunctive semaglutide was associated with improvements in HRQoL in adults with MDD. Associations with metabolic and motivational changes were observed but should be interpreted as exploratory. These findings support further investigation of metabolic interventions targeting patient-centred outcomes in depression.

37. MEK Inhibition in Fragile X Syndrome: Preclinical Evaluation for Therapeutic Potential

Demi Ma, BSc [[1]-[3]], Asim Ahmed, MSc [[1]], Bosong Wang, MSc [[1]], Crystal Luu [[1]], BSc, Diana Shehu, BSc [[1]], Ning Cheng, PhD [[1]-[3]] [1]Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada. [2]Alberta Children's Hospital Research Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada. [3]Faculty of Veterinary Medicine, University of Calgary, Calgary, Alberta, Canada.

Introduction: Fragile X Syndrome (FXS) is the leading monogenic cause of autism spectrum disorder. It is characterized by loss of a functional protein, FMRP, and hyperactivation of extracellular signal-regulated kinase (ERK) signaling. While repurposed drugs indirectly modulate this pathway, whether direct upstream ERK inhibition, via MEK, can improve FXS phenotypes remains untested. PD325901 (Mirdametinib) is a potent, brain-penetrant MEK1/2 inhibitor recently FDA-approved for Neurofibromatosis Type 1, a related RASopathy, making it a compelling repurposing candidate for FXS.

Methods: Wildtype and fmr1 knockout (KO) FVB mice received acute (i.p., 25 mg/kg) or chronic (drinking water, from postnatal day 7) PD325901. Target engagement was assessed by Western blot measuring pERK/ERK across brain regions. Behavioural outcomes, including locomotion, anxiety, sociability, and recognition memory, were assessed across both sexes under chronic treatment.

Results: Acute PD325901 robustly reduced ERK phosphorylation across multiple brain regions in wildtype and fmr1 KO males, confirming reliable CNS target engagement. Behaviourally, acute treatment normalized locomotor hyperactivity and exploratory behaviour in KO males to wildtype levels. Chronic treatment enhanced recognition memory behaviour in female fmr1 KO mice and social novelty preference in males, with no adverse effects on locomotion or anxiety-like behaviour observed in either sex, suggesting domain- and sex-specific gains without broad behavioural disruption.

Conclusions: PD325901 engages its molecular target in the FXS brain and produces meaningful behavioural rescue across multiple domains. These findings provide strong proof-of-concept for MEK inhibitor repurposing in FXS and advance the translational pipeline toward accessible, effective pharmacotherapy for neurodevelopmental disorders, especially by highlighting biological sex differences.

38. Distinct Brain-Behaviour Relationships are Associated with Cognitive Dysfunction in Substance Use Disorders: A Multivariate Approach

Nafia Mirza ([1,2])., Priya V.O ([1,2])., Justin N ([1,2])., Thomas T ([2])., Lena C.Q ([2,3])., Erica Vieira ([2,4]), Thomas P ([2,4,5]), Daphne V ([1,2,4]), Daniel F. ([1,2,4],6), Anthony C.R ([2,3])., Colin H ([1,2,4]), Yuliya S. N ([1,2,4]). [1]) Institute of Medical Science, University of Toronto, Toronto, ON, Canada. [2]) The Centre for Addiction and Mental Health, Toronto, ON, Canada. [3]) Department of Psychology, University of Toronto Scarborough, Toronto, ON, Canada. [4]) Department of Psychiatry University of Toronto, Toronto, ON, Canada. [5]) Department of Pharmacology and Toxicology University of Toronto, Toronto, ON, Canada. 6) Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada.

Introduction: Substance use disorders (SUDs) are associated with impairments in higher-order cognitive processes such as executive functioning (EF). Prior neuroimaging work associates SUDs with decreased cortical thickness in EF-related regions. However, few studies have directly linked cognition to structural neuroimaging data, particularly in naturalistic samples that reflect the complexity of real-world SUD populations. The purpose of the study is to examine the association between brain structure and cognitive function using a multivariate approach in a complex heterogeneous sample of adults with diverse SUDs.

Methods: A preliminary sample of participants (n = 113, 31% Female) seeking treatment for any SUD was drawn from the ongoing Cognitive Dysfunction in Addictions (CDiA) study. Cognitive measures included standardized domain scores from CNS Vital Signs. Cortical thickness and subcortical volume measures were derived from structural MRI collected at the Centre for Addictions and Mental Health (CAMH). Partial least squares correlation (PLSC) was used to identify latent patterns linking brain structure and cognitive performance.

Results: Two significant latent variables emerged. LV1 demonstrated an association between EF and cortical thickness in frontotemporal and cingulate regions, consistent with established executive control networks. LV2 reflected a distinct psychomotor and motorspeed–related

pattern, with contributions from visual and insular regions. No subcortical volume measures survived bootstrap thresholding.

Conclusion: Multivariate approaches reveal distinct brain–behavior relationships in SUDs, characterized by separable cortical networks without corresponding subcortical involvement. These findings highlight the heterogeneity of cognitive dysfunction and may inform targeted interventions.

39. Longitudinal [18F]SynVesT-1 PET Imaging of Synaptic Development in Adolescent Cannabis Users: Preliminary Findings from the TAY Cohort Study

Vivian Mohn, Cassie Côté, Maia Zilberman, Lujia (Ember) Yu, Jennifer Truong, Yuliya Nikolova, Erin Dickie, Stephanie H. Ameis, Kimberly Desmond, Lucas Narciso, Carme Uribe, Dafna Kahana, Neil Vasdev, Daniel Felsky, Benjamin Goldstein, Kristin Cleverley, Darren Courtney, Lisa Hawke, Nicole Kozloff, Alexia Polillo, Martin Rotenberg, Lena C. Quilty, Wei Wang, George Foussias, Aristotle Voineskos, Jerry Warsh, M. Omair Husain, Isabelle Boileau, and TAY Cohort Study Team

Introduction: Lower synaptic density has been observed in adult cannabis users, but it remains unclear how cannabis use patterns influence synaptic changes over time, particularly during adolescence. PET radiotracers for synaptic vesicle glycoprotein 2A (SV2A) can be used as in-vivo markers of synaptic density. In this study, we use longitudinal [18F]SynVesT-1 PET scans to compare synaptic development trajectories in adolescent cannabis users versus non-users, hypothesizing distinct patterns of change between groups.

Methods: Youth seeking mental health treatment aged 16-24 were recruited from the Toronto Adolescent and Youth (TAY) Cohort Study, completing two [18F]SynVesT-1 PET scans at least one year apart, with a baseline MRI to delineate six regions of interest. A simplified reference tissue model 2 (SRTM2) with the centrum semiovale as a pseudo-reference region was used to fit time activity curves and calculate non-displaceable binding potential (BPND). Past 90 days of self-reported cannabis consumption was collected at both scans to determine cannabis usage.

Results: 30 participants (14M, 16F, mean age 20.39±2.7) were included in analyses. Across all participants, whole brain BPND significantly declined over time ($F(1,29)15.34$, $p = 0.001$, -9% decrease). Cannabis users (n = 16) experienced smaller changes in BPND compared to non-users (n = 14) in the anterior cingulate cortex ($p = 0.025$), hippocampus ($p = 0.041$), amygdala ($p = 0.031$), temporal cortex ($p = 0.049$), striatum ($p = 0.045$), and prefrontal cortex (non-significant, $p = 0.052$).

Conclusion: We found that adolescent cannabis users experienced significantly less decline in synaptic density over time compared to non-users, as measured with [18F]SynVesT-1 PET. Our sample including youth with mental illness will be increased in future work. These preliminary findings warrant further investigation into how changes in synaptic density over time are impacted by cannabis use, and how synaptic development relates to adolescent mental health.

40. Investigating Social Stress Response and Brain Fatty Acid Amide Hydrolase Levels in Social Anxiety Disorder: A Multimodal Imaging Investigation using the Montreal Imaging Stress Task and PET Imaging with [11C]CURB

Christina F. Pereira, HBSca,b, Maria T. Secara, HBSca,b,, Rheina Firdiawati, HBSca,d, Pablo M. Rusjan, PhDf, Rachel F. Tyndale, PhDa,d,e, M. Ishrat Husain, MDa,b,e, Jerry Warsh, MDa,b,e, Bernard Le Foll, MD, PhD.a-e,g, Gwyneth Zai, MD, PhDa,b,d,e, Colin Hawco, PhDa,b,, Isabelle Boileau, PhDa,b,d,e, Stefan Kloiber, MDa,b,d,e

Introduction: Social anxiety disorder (SAD) is an impairing condition. The Montreal Imaging Stress Task (MIST) combines high cognitive demand with negative social evaluation. Research implicates the endocannabinoid enzyme fatty acid amide hydrolase (FAAH) in stress response. This analysis evaluated MIST response between SAD and healthy controls (HCs) and the relationship with brain FAAH levels using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET).

Methods: Individuals with SAD (n=17;M/F=7/10;age:25.33±5.89) and HC (n=24;M/F=11/13;age:24.50±4.62) completed three conditions of the MIST (sensorimotor control condition, low stress condition, and psychosocial stress condition) and self-reported ratings of stress. [11C]CURB PET scanning measured brain FAAH at rest. Contrasts between the psychosocial stress and sensorimotor control conditions were assessed in the amygdala, hippocampus, and anterior cingulate cortex (ACC) and compared across groups (SAD vs. HC) using a RM-ANCOVA, controlling for age, sex, and motion. Associations between brain activity, stress ratings, and brain FAAH were evaluated controlling for FAAH genotype.

Results: HCs showed significant deactivation in the hippocampus during psychosocial stress condition vs sensorimotor control (right:p=0.017;left:p=0.042), while there was no difference in SAD. There was no overall group difference (F(1,34)=1.75;p=0.195), but right amygdala response was greater in SAD compared to HCs(p=0.026). Functional response was not correlated with FAAH levels (p>0.05). Stress ratings were higher in SAD but did not reach significance (F(1,22)=3.797;p=0.064). Stress ratings were not correlated with FAAH in the pooled or HC sample (p>0.05). In the SAD group, feelings of stress (r=0.712,p=0.006) and worry (r=0.656;p=0.015) were positively correlated with hippocampal FAAH.

Conclusion: This preliminary analysis evaluated the relationship between brain FAAH and social stress response. SAD and HCs demonstrated differential MIST response in the amygdala, but this was not associated brain FAAH at rest. In line with previous research, ratings of stress and worry were positively associated with hippocampal FAAH in SAD.

41. Multi-Trait GWAS and Multimodal Single-Cell Regulatory Mapping Reveal Novel Cell-Type-Specific Molecular Mechanisms Underlying Smoking Behaviours and Schizophrenia (submitted and accepted but not presented)

Jennie G. Pouget, MD PhD[1,2,3], Suzan Farhang-Sardroodi, PhD[1], Saori Sakaue, MD PhD[4,5], Kathryn Weinand, PhD[4], Soumya Raychaudhuri, MD PhD[4],6,7, Rachel F. Tyndale, PhD[1,2,3], Meghan J. Chenoweth, PhD[1,2,3] [1]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada [2]Department of Psychiatry, University of Toronto, Toronto, ON, Canada [3]Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada [4]Brigham and Women's Hospital, Boston, Massachusetts, USA [5]Department of Genome Sciences, University of Washington, Seattle, Washington, USA 6Broad Institute, Boston, Massachusetts, USA 7Harvard Medical School, Boston, Massachusetts, USA

Introduction: Tobacco smoking and schizophrenia are highly comorbid, heritable, and genetically correlated traits. Elucidating shared molecular mechanisms may help prioritize

biological pathways for future therapeutic development, given that pharmacological targets supported by human genetic evidence are over two times more likely to succeed in clinical trials.

Methods: We analyzed genome-wide association study (GWAS) summary statistics for two smoking phenotypes (cigarettes per day, CigDay; smoking cessation, SmkCes) and schizophrenia using Multi-Trait Analysis of GWAS (MTAG), which increases statistical power. We fine-mapped novel MTAG loci using approximate Bayes factor to estimate posterior inclusion probabilities and 90% credible sets. To construct cell-type-specific enhancer-gene maps, we analyzed multimodal single-nucleus sequencing data (10x Genomics) for dorsolateral prefrontal cortex using SCENT. To identify putative cell-type-specific mechanisms underlying novel MTAG loci, we intersected fine-mapped variants with our SCENT enhancer-gene maps.

Results: Compared to the original single-trait GWAS, MTAG increased discovery for smoking behaviours, identifying 46 novel loci for CigDay and 28 for SmkCes. Our single-cell analyses identified two novel MTAG loci for CigDay localizing to candidate cis-regulatory elements (cCREs) in DLPFC. Two tightly linked SNPs on chromosome 14 were located within a putative excitatory neuron-specific silencer (SCENT ß=-0.05, FDR=0.06) for CKB. CKB encodes brain-type creatine kinase, an enzyme selectively expressed in the brain and involved in energy homeostasis. At another locus on chromosome 19, a set of tightly linked SNPs both mapped to independent putative excitatory neuron-specific enhancers for SLC8A2 (ß=0.06, FDR=0.09 and ß=0.06, FDR=0.02), which encodes a neuronal sodium-calcium exchanger implicated in synaptic signaling. Both cCREs showed broader regulatory effects, linked to MEIS3, C5AR1, and TMEM160 expression in addition to SLC8A2.

Conclusions: Integrating MTAG with multimodal single-cell data improved genomic discovery and refined biological interpretation of loci associated with smoking behaviours. Our findings implicate excitatory neuron-specific regulatory mechanisms and prioritize disease-relevant genes for mechanistic follow-up.

42. Insomnia Polygenic Risk Meets Cardiovascular Risk: Insights from a Clinical Sample of Youth with Bipolar Disorder

Alexandra A. Puchiele, BMSc Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, Ontario, Canada. Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada Megan Mio, PhD, Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, Ontario, Canada Clement C. Zai, PhD, Center for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, Ontario, Canada. Institute of Medical Science, University of Toronto, Toronto, Ontario Canada. Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada. Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada. Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada. Benjamin I. Goldstein, MD PhD, Center for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, Ontario, Canada. Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada. Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada. Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada.

Introduction: Insomnia is common in bipolar disorder (BD) and increases risk of cardiovascular disease (CVD). Insomnia polygenic risk (insomnia-PRS) is associated with BD and CVD in adults, however this remains underexplored in youth. The current study examined the extent to which insomnia-PRS relates to cardiovascular risk in youth with and without BD. We

hypothesized that higher insomnia-PRS would be associated with greater cardiovascular risk in the overall sample, particularly in youth with BD.

Methods: Participants included 173 youth (98 BD, 75 controls), aged 13-20 years. Insomnia-PRS was computed using adult insomnia genome-wide association study summary statistics. A composite cardiovascular risk score (range: 0-6) was derived from categorization of body mass index (BMI), systolic and diastolic blood pressure. Linear regressions examined the association of insomnia-PRS with cardiovascular risk scores, controlling for age, sex, current mood, and the first two genetic principal components. Secondary analyses examined diagnostic differences (BD vs. controls) and individual cardiovascular risk factors.

Results: Insomnia-PRS was not significantly associated with cardiovascular risk scores in the overall sample (p=0.07, ß=0.14). In diagnostic subgroups, higher insomnia-PRS was associated with higher cardiovascular risk scores in youth with BD (p=0.007, ß=0.28), but not in controls (p=0.37, ß=-0.11). In secondary analyses examining individual cardiovascular risk factors, higher insomnia-PRS was associated with higher BMI (p=0.045, ß=0.20) and mean arterial pressure (p=0.02, ß=0.25) in youth with BD, but not in controls. Findings were not significant after Bonferroni correction.

Conclusion: This study provides preliminary evidence that polygenic risk for insomnia is associated with cardiovascular risk factors in youth with BD. These results suggest a potential link between genetic susceptibility to insomnia and cardiovascular risk in BD that warrants replication in larger, prospective samples. Adolescence may represent a critical developmental window for investigating early mechanisms underlying cardiovascular risk in BD.

43. Association Between Plasma Adipokines and Depression Severity in Community-Dwelling Older Adults

Sara Rezaei, PhD: University of Toronto/CAMH, Toronto, Canada Ully Aléxia Caproni Corrêa, MSc: Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil Leani Souza Máximo Pereira, PhD: Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil Natália Reinaldo Sampaio, MSc: Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil Taís Gonçalves Soares, PhD: Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil Silvia Lanziotti da Silva, PhD: Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brazil Antonio Lucio Teixeira, PhD: University of Texas Health Science Center at San Antonio, San Antonio, TX, USA. Daniele Sirineu Pereira, PhD: Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil Érica Vieira, PhD: University of Toronto/CAMH, Toronto, Canada

Introduction: Late-life depression has been associated with systemic inflammatory and metabolic dysregulation. Adipokines such as leptin, resistin, and adiponectin may contribute to biological pathways involved in depression; however, their relationship with depressive symptom severity in older adults remains incompletely understood. We investigated associations between circulating adipokines and depressive symptom severity in community-dwelling older adults, hypothesizing that depressive symptoms would be associated with elevated pro-inflammatory adipokines.

Methods: This exploratory, population-based study included 373 community-dwelling older adults aged 60 years or older (142 men, 231 women) recruited in city of Alfenas, state of Minas Gerais, Brazil. Blood samples were collected at baseline, and plasma adiponectin, leptin, and

resistin levels were quantified using enzyme-linked immunosorbent assays (ELISA). Depressive symptom severity was assessed using the Geriatric Depression Scale (GDS) at baseline and one-year follow-up. Partial Spearman correlation analyses adjusted for age and sex were performed to evaluate associations between adipokine levels and GDS scores.

Results: Participants with depression exhibited higher circulating leptin (p=0.0016) and resistin (p=0.0092) levels compared to non-depressed participants at baseline, while adiponectin levels did not differ between groups (p=0.394). Partial Spearman correlation analyses adjusted for age and sex demonstrated a positive association between leptin levels and baseline GDS scores (?=0.12, p=0.02). Resistin levels were positively associated with GDS scores at both baseline (?=0.125, p=0.014) and follow-up (?=0.129, p=0.019).

Conclusion: Elevated circulating leptin and resistin levels were associated with greater depressive symptom severity in community-dwelling older adults. The consistent association between resistin and depressive symptoms across timepoints may support a role for inflammatory-metabolic signaling in late-life depression. Further longitudinal studies are needed to clarify the mechanistic and clinical relevance of adipokines in depression during aging.

44. Comparative Neurophysiological Signatures of Psychedelics, Stimulants, and Anesthetics in Rodent Cortical Activity

Brandon Richardson, MSc[1], Jordan O'Byrne, PhD[2], Vitor Bruno, PhD[1], Stefano Comai, PhD[1]?[3], Robin L. Carhart-Harris, PhD[4], Gabriella Gobbi, MD, PhD[1]?[5] [1] Neurobiological Psychiatry Unit, McGill University, Montreal, Quebec, Canada [2] Department of Psychology, Université de Montréal, Montreal, Quebec, Canada [3] Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Padova, Italy [4] Psychedelics Division, Neuroscape, Department of Neurology, University of California San Francisco, San Francisco, California, United States [5] Research Institute, McGill University Health Centre, Montreal, Quebec, Canada

Introduction: Serotonergic psychedelics are known to produce profound alterations in conscious experience through 5-HT2A receptor agonism, yet their specific large-scale neurophysiological signatures remain incompletely defined relative to other pharmacological states. The objective of this study was to determine whether classical psychedelics exhibit a distinct cortical electrophysiological signature compared with stimulants, atypical psychedelics, and anesthetics.

Methods: 50 adult male Sprague-Dawley rats (postnatal day 60–70) were implanted with epidural electrocorticography (ECoG) and electromyography (EMG) electrodes. Recordings were acquired during a 6-hour post-administration period following intraperitoneal injection of psilocybin (6 mg/kg), LSD (0.2 mg/kg), 5-MeO-DMT (10 mg/kg), lisuride (0.5 mg/kg), d-amphetamine (5 mg/kg), or propofol (100 mg/kg). Neural activity was analyzed in 10-minute windows using spectral power decomposition, Lempel–Ziv complexity, Higuchi fractal dimension, and spectral entropy. Group differences were assessed using mixed-effects models, and multivariate structure was evaluated using principal component analysis (PCA) and clustering.

Results: Classical psychedelics (psilocybin, LSD) significantly reduced alpha, beta, and low-gamma power ($p < 0.05$), reflecting widespread high-frequency desynchronization. In contrast, 5-MeO-DMT, lisuride, and d-amphetamine increased delta and low-gamma power ($p < 0.05$).

Propofol selectively increased alpha power without broader spectral changes. Temporal complexity measures (Lempel–Ziv, Higuchi fractal dimension) showed no consistent cross-compound effects. Spectral entropy revealed selective increases in delta-band entropy across all drugs ($p < 0.05$), with d-amphetamine additionally increasing beta and low-gamma entropy. PCA (71.08% variance explained) and clustering showed clear separation of psychedelics, stimulants, and propofol, with intermediate overlap for 5-MeO-DMT and lisuride.

Conclusion: Classical psychedelics are defined by reduced high-frequency power and increased delta-band entropy, indicating a low-power, desynchronized cortical state. While sharing delta entropy with d-amphetamine, they are clearly separated by opposite effects on overall cortical activation. Clinically, this suggests psychedelics do not increase global complexity but induce frequency-specific desynchronization of cortical oscillations that may underlie their therapeutic efficacy.

45. In Vivo Imaging Brain Monoamine Oxidase B - an astrocytic marker - in Cannabis Use Disorder

Christian Ramos-Jiménez, M.D.,[1,2] M. Belen Blasco, M.D.,[1,2] Johan Cohen, M.D.,[2] Daniel Chartrand, M.D., Ph.D.,[3] Gassan Massarweh, Ph.D.,[4] Pablo M. Rusjan, Ph.D.,[2,5] Romina Mizrahi, M.D., Ph.D.[1,2,5]

[1]Clinical and Translational Sciences Lab, Douglas Research Centre, Montreal, Quebec, Canada
[2]Douglas Research Centre, Department of Psychiatry, McGill University, Montreal, Quebec, Canada
[3]Department of Anesthesia, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada
[4]McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada
[5]Department of Psychiatry, McGill University, Montreal, Quebec, Canada

Introduction: Cannabis use disorder (CUD) is highly prevalent and lacks validated biomarkers. Although emerging evidence implicates astrocytic dysfunction in the neurobiology of addiction, it remains unknown whether in vivo monoamine oxidase B (MAO-B) levels, an index of astrocyte function, are altered in CUD. We determined whether MAO-B levels are lower in cannabis users and CUD, and examined associations with cannabis exposure, severity and craving.

Methods: A total of 25 cannabis users (23 of them with CUD) and 19 healthy controls were studied. MAO-B levels were quantified using high-resolution [^{11}C]SL25.1188 Positron Emission Tomography (PET) with arterial blood sampling across prioritized brain regions of interest delineated in individual magnetic resonance images. Cannabis use was confirmed with urine drug screens. Cannabis exposure, dependence and craving were evaluated using the Durg History Questionnaire, the Marihuana Craving Questionnaire and the Severity Dependence Scale.

Results: MAO-B levels were significantly lower in cannabis users (n=25; $F_{1,50.47}$=14.74, p<0.001, Cohen's F=0.54; ROI effect: $F_{6,65.82}$=425.24, p<0.001), with larger effects in individuals with CUD (n=23; $F_{1,48.51}$=16.73, p<0.001, Cohen's F=0.59; ROI effect: $F_{6,64.01}$=410.55, p<0.001). Lower MAO-B levels were associated with greater cannabis exposure in the past year ($F_{1,26.60}$=10.18, p=0.004, Cohen's F=0.62) and greater cannabis craving ($F_{1,27.57}$=7.92, p=0.009, Cohen's F=0.54), but not with severity of dependence (severity of dependence: $F_{1,26.68}$=0.04,

p=0.85, Cohen's *F*=0.04) or severity of cannabis withdrawal symptoms ($F_{1,26.79}$ = 1.38, *p* = 0.25, Cohen's *F* = 0.23).

Conclusion: Lower MAO-B levels are present in cannabis users and CUD and are associated with greater cannabis exposure and craving.

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46. Quantification of [^{18}F]TRACK, a radioligand for Tropomyosin Receptor Kinases, without arterial canulation.

Christian Ramos-Jiménez[1,2], Chris Hung-Hsin Hsiao[3], Robert Hopewell[3], Gassan Massarweh[3,4], Jean-Paul Soucy[3,4], Daniel Chartrand[3,5], Alexey Kostikov[3,4,6], Alexander Thiel[4,7], Pablo M Rusjan[2]

[1]Clinical and Translational Sciences Lab, Douglas Research Centre, Montreal, H4H 1R3, Quebec, Canada
[2]Douglas Research Centre, Department of Psychiatry, McGill University, Montreal, Quebec H3A 1A1, Canada
[3]McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Quebec H3A 2B4, Canada
[4]Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec H3A 2B4, Canada
[5]Department of Anesthesia, Montreal Neurological Institute, McGill University, Montreal, Quebec H3A 2B4, Canada
[6]Department of Chemistry, McGill University, Montreal, Quebec, H3A 0B8, Canada
[7]Jewish General Hospital and Lady Davis Institute for Medical Research, Montreal, Québec H3T 1E2, Canada

Introduction: We recently introduced [^{18}F]TRACK, a radioligand that binds to tropomyosin receptor kinases B and C (TrkB/C). Kinetic modeling with arterial input function showed Multilinear Analysis 1 (MA1) as the preferred method to obtain V_T. After a bolus administration, transient equilibrium (TE) between tissue and metabolite-corrected plasma was reached at ~70min. In this work, we explore the use of a single venous sample at TE to calculate the apparent V_T^{app}. For 1TCM, V_T^{app} overestimates V_T by a factor $1/(1-bV_T/K_1)$ where β is the clearance of radiotracer from tissue and plasma at TE. A tissue clearance corrected (TCC) $V_T^{tcc}=V_T^{app}/(1+ gbV_T^{app})$ was proposed (Hillmer, JCBFM 2020) measuring β from the tissue clearance and with g being a regional ligand-specific constant. This work compares the agreement among these total distribution volumes with the aim of identifying reliable approaches for accurate Trk receptor quantification without arterial cannulation.

Methods: Six healthy volunteers (male=5, female=1; age: 22-45 years) were scanned in a High Resolution Research Tomograph for 90min after an I.V. bolus injection of [^{18}F]TRACK (0.18-1.73μg, 3.2-6.4mCi). Regional V_T values were estimated with MA1 using **arterial input** function. V_T^{app} values were calculated at 75 min using the concentration of unmetabolized [^{18}F]TRACK in a **venous plasma sample**. Tissue activity was corrected for a 4% of vascular contribution. Regional γ values were set to 1/average K_1, with K_1 values obtained from a previous study. β was calculated from the gray matter TAC from 70 to 90 min.

Results: V_T^{app} and V_T^{tcc} correlated well with V_T (r^2=0.72-0.95 and r^2=0.74-0.89 respectively) but overestimated it by 53% and 20%, respectively across ROIs. Consistency measured using the interclass correlation coefficient ICC(3,k) improved with the tissue clearance correction from 0.81-0.92 to 0.92-0.97 (Figure).

Conclusion: Venous based TCC V_T^{tcc} showed excellent consistency with V_T and represents a promising approach to quantify [^{18}F]TRACK. Further work will focus on the optimization of the g values.

47. Medical Cannabis Use in Autism: Insights from an Israeli HMO on Patient Characteristics and Alignment with National Guidelines (Submitted and accepted but not presented)

Hadar Sadeh [1 2], Talish Razi [3], Ronen Arbel [3 4], Doron Netzer [3 5], Gal Meiri [1 2 6]

1. Child and Adolescent Psychiatry Unit, Soroka University Medical Center, Beer Sheva, Israel.
2. Psychiatry Division, Faculty of Health Science, Ben Gurion University of the Negev, Beer Sheva, Israel.
3. Community Medical Services Division, Clalit Health Services, Tel Aviv, Israel.
4. Maximizing Health Outcomes Lab, Sapir College, Sderot, Israel.
5. Adelson School of Medicine, Ariel University, Tel Aviv, Israel.
6. Azrieli National Center for Autism and Neurodevelopment Research, Ben Gurion University of the Negev, Beer Sheva, Israel.

Background and Objective: Evidence for medical cannabis use and effectiveness in autism has begun to accumulate but remains limited, even as clinical interest has rapidly increased. In Israel, medical cannabis may be prescribed for autism with severe behavioral disturbances under strict Ministry of Health criteria requiring prior trials of two Food and Drug Administration (FDA)-approved antipsychotics. Using a large real-world dataset, this study aimed to characterize autistic individuals prescribed medical cannabis and evaluate adherence to national guidelines.

Methods: A retrospective cohort study was conducted using electronic medical records from Clalit Health Services, Israel's largest Health Maintenance Organization. All individuals with a documented autism diagnosis between 1990 and 2025 were identified (N = 36,610) and classified as cannabis-prescribed (N = 462) or not-prescribed (N = 36,148). Demographic and clinical characteristics were compared, including prior use of FDA-approved antipsychotics.

Results: Only 1.2% of individuals with autism were prescribed medical cannabis. Of these, 4.3% of prescriptions were issued for children under 5 years of age. The cannabis-prescribed group was diagnosed earlier (median 3 vs. 5 years, $p < 0.001$) and had higher rates of ADHD (42% vs. 30%), intellectual disability (12% vs. 5%), and epilepsy (14% vs. 6%) (all $p < 0.001$). While 69% had used at least one FDA-approved antipsychotic medication prior to cannabis initiation, only 28% had documented trials of both, as required by national guidelines. Marked sociodemographic disparities were also observed: the cannabis-prescribed group had a higher

socioeconomic status (median SES 7 vs. 6, $p < 0.001$) and lower representation of Arab individuals (2.7% vs. 11%, $p < 0.001$).

Conclusions: Medical cannabis use among autistic individuals was rare and mainly observed among those with more complex clinical profiles and higher socioeconomic backgrounds. Most prescriptions did not fully comply with guidelines requiring prior antipsychotic trials. These findings underscore the need for enhanced regulatory oversight, equitable access, and longitudinal research to evaluate real-world outcomes and guide evidence-based clinical practice.

48. In vivo characterization of strain-specific entourage effects in Psilocybe mushrooms in a rat model of autism

Stefan M. Salo, PhD candidate, Joshua D. Manduca, MSc, Leah M.A. Anderson, BSc, Ashe G. Mueller, Andrew M.P. Jones, PhD, Melissa L. Perreault, PhD Department of Biomedical Sciences, University of Guelph, Guelph, Ontario, Canada

Introduction: Whole psilocybin mushrooms contain additional bioactive compounds that may be capable of producing strain-specific “entourage effects”. This study examined whether chronic microdosing with two distinct Psilocybe strains (P1 or P3) in rats have therapeutic properties that differ from purified psilocybin (PSB) in the valproic acid (VPA) rat model of autism.

Methods: VPA-exposed rats consumed daily microdoses of PSB (0.3 mg/kg), P1 or P3 (PSB equivalent) for 31 days starting on postnatal day (PND) 22. Anxiety-like (elevated plus maze), repetitive (grooming, marble burying), and social (three-chamber) behaviours, as well as recognition memory were evaluated from PND 35-43. Local field potentials were recorded (PND 52) from the medial prefrontal cortex (PFC) and dorsal hippocampus (dHIP), among others (not shown). Spectral power and coherence were analyzed.

Results: VPA-animals displayed autism-like behavioural alterations across multiple measures. All treatments improved some aspects of these deficits, producing distinct efficacy profiles with sex- specific effects. VPA only altered repetitive behaviours in male rats, and these were normalized selectively by P1. All 3 treatments improved sociality and/or social preference, with P1 having the most robust effects, particularly in the males. PSB and P1, but not P3, improved VPA-induced anxiety in male rats with no effect in females. The treatments also improved VPA-induced deficits in recognition memory. PSB and P1 selectively normalized the upregulation of PFC and dHIP theta power in male rats. However, treatments did not suppress PFC or dHIP theta power in the females, with the exception of P1. PSB and P1 improved dHIP high gamma power alterations in the males. Further, PSB normalized the VPA-induced suppression of PFC-dHIP high-gamma coherence in male rats only.

Conclusion: Chronic microdosing with whole psilocybin mushrooms produces strain-specific behavioural and neuronal oscillatory signatures that differ from purified PSB in VPA rats, demonstrating that whole mushroom chemistry may meaningfully shape therapeutic outcomes in autism.

49. Exercise Doesn't Feel the Same for Everyone: Depression Severity Predicts Physical Exhaustion Responses to Single-Session Aerobic Exercise in Youth with Bipolar Disorder

Bridget S.M. Siek, BSc[1,2]; Mikaela K. Dimick, PhD[1]; Bradley J. MacIntosh, PhD[1,3,4]; Benjamin I. Goldstein, MD, PhD[1,2,5] [1] Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, ON, Canada; [2] Department of Pharmacology, University of Toronto, Toronto, ON, Canada; [3] Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada [4] Heart and Stroke Foundation Canadian Partnership for Stroke Recovery, Sunnybrook Research Institute, Toronto, ON, Canada; [5] Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Introduction: Exercise participation is low in bipolar disorder (BD), despite potential benefits on physical and mental health. We set out to build on prior findings by examining individual variability in the effect of a single exercise session on subjective physical exhaustion among youth with BD.

Methods: Fifty-two youth with BD (17.3±1.3 years) completed semi-structured diagnostic interviews (K-SADS-PL). Depression severity was evaluated using the K-SADS depression rating scale (DRS) to assess severity of overall depression symptoms and individual depression symptoms (depressed mood, irritability, anhedonia, fatigue). The Exercise-Induced Feeling Inventory was administered before and after a 20-minute moderate-intensity stationary cycling session at 70% of age-predicted maximum heart rate. K-means clustering was used to identify subgroups based on changes in a physical exhaustion (?PE=post-pre) subscale of the Exercise-Induced Feeling Inventory. Group differences in demographic and clinical variables were assessed using chi-squared tests and ANOVA or Kruskal-Wallis tests. Bonferroni adjustment was applied to correct for multiple comparisons.

Results: K-means clustering identified three groups: no change (n=22; ?PE -0.67 to 0.67), improved (i.e., reduced physical exhaustion post-exercise) (n=14; ?PE -2.00 to -1.00), worsened (i.e., increased physical exhaustion post-exercise) (n=16; ?PE 1.00 to 2.33). There were no significant differences in demographic characteristics across groups. Compared to the worsened group, the improved group had greater pre-exercise overall depression symptom severity (p=0.02), irritability (p=0.04), anhedonia (p=0.03), and fatigue (p=0.02).

Conclusion: Greater depression severity among youth with BD was associated with reduced physical exhaustion following exercise. Although depression symptoms are known barriers to exercise, these findings suggest that youth with greater depression symptom burden may experience more favorable changes in physical exhaustion. Future work integrating neuroimaging is warranted to elucidate the mechanisms underlying the improved exhaustion among youth experiencing more severe depression symptoms. Present findings also have potential implications for psychoeducation and exercise trial design in this population.

50. Effects of a single psilocybin exposure on whole-brain c-Fos expression and prolonged anxiety-like behaviour in male and female rats

Sikic A[1], MSc, Sfiligoi CE[2], Greswell VC[1], Peart DR[1], MSc, & Murray JM[1], PhD
[1]Department of Psychology, University of Guelph, Guelph, ON, Canada; [2]Department of Molecular and Cellular Biology, University of Guelph, Guelph, ON, Canada

Introduction: Clinical studies have recently demonstrated promising therapeutic effects of a single psilocybin exposure for various psychiatric conditions; however, comparatively little preclinical work has characterized the persistent behavioural consequences of psilocybin exposure in rats. While acute pharmacological and neural effects are increasingly understood, whole-brain functional connectivity in the rat as well as longitudinal behavioural trajectories following a single psilocybin exposure remain underexplored.
Methods: Here, we present complementary pilot investigations examining both the acute neural and persistent anxiety-like effects of psilocybin in rats. In one study, animals received a high dose (5 mg/kg) of psilocybin and were perfused 2h later to assess brain-wide c-fos activation reflective of peak drug effects. In a separate study, animals received a single psilocybin administration spanning a range of doses (0.1, 1, 3, 5, or 10 mg/kg) and were acutely evaluated for behavioural markers of serotonin receptor 2A activation. Additionally, animals were assessed for anxiety-like behaviour on the elevated plus maze (EPM) prior to drug exposure and repeatedly once per week for four weeks post-administration.

Results: Preliminary c-Fos data from the prelimbic (PLC) and infralimbic (ILC) cortices, the dorsomedial striatum (DMS), and the nucleus accumbens shell (NAcSh) suggest a functional decoupling of PLC-NAcSh and ILC-NAcSh connectivity under psilocybin. Behaviourally, psilocybin dose-dependently increases the number of head-twitch responses, wet-dog shakes, and defecation, while decreasing time spent rearing and grooming. EPM data suggest increased open arm exploration compared to that of controls at days 10 and 17 post-exposure.

Conclusions: Our findings suggest psilocybin may have anxiolytic properties that persist for 10-24 days following a single exposure in rats. Additionally, c-Fos data suggest that psilocybin acutely decreases functional connectivity of typically coupled brain regions. Together, these investigations provide preliminary characterization of both the acute systems-level neural effects and longer-term behavioural consequences of single psilocybin exposure in rats.

51. A neuronal waveform classification assay to characterize inhibitory and excitatory bursting in MEA data: Erinacine A as a model drug

Evan T. Spangenberg and Dr. Melissa L. Perreault

Introduction: Erinacine A (EA), the primary bioactive compound of the nootropic mushroom Lion's mane (Hericium erinaceus), is a potent stimulator of growth factor synthesis demonstrated to influence neuronal activity, yet its specific effects on cortical network dynamics remain uncharacterized. This study investigated whether EA produces sex and neuron-type dependent shifts in cortical excitatory/inhibitory (E/I) activity, and whether multielectrode array (MEA)-based neuron-type classification can resolve these changes at a level inaccessible to aggregate analysis.

Methods: Rat cortical neurons derived from were cultured on MEA plates. EA was administered at 0, 10nM, 100nM, and 1μM, and activity assessed at both single-neuron and network levels after 24h through spike sorting and waveform analysis. Neurons were classified into 5 groups, including putative inhibitory (PI) and putative excitatory (PE) classes, using a novel classification script.

Results: At 100nM, aggregate analysis indicated a female-specific increase in mean firing rate and burst number while males did not, suggesting a female-dominant EA response. However, PE/PI classification revealed that population-level metrics obscure fundamentally different E/I

dynamics between sexes. In females, PI neurons shifted toward tonic firing as evidenced by decreased burst duration, spikes per burst, and interspike interval (ISI) coefficient of variation (CoV). This produced sustained inhibitory output that maintained synchrony and generated frequent and well-coordinated network bursts to preserve E/I balance under increased excitatory activity. In males, EA increased PE burst frequency while PI neurons showed increased ISI and spike amplitude. This indicated stronger but less frequent inhibitory events that failed to match excitatory activity, producing E/I imbalances that were reflected by decreased synchrony and longer, stereotyped, repetitive network bursting with reduced CoV2, indicative of reduced inhibitory efficacy.

Conclusion: These findings demonstrate that classifying neurons into PE and PI subpopulations reveals compound-induced E/I shifts that aggregate MEA analysis cannot detect, validating this approach for preclinical neuroactive compound screening.

52. Long-term stability of individual differences in 50-kHz ultrasonic vocalizations in female rats: effects of estrous cycle

Adithi Sundarakrishnan, BSc, Bridget Siek, BSc, Olivia Gundra, and Paul B.S. Clarke, PhD. Department of Pharmacology & Therapeutics, McGill University, Montre´al, QC, Canada.

Introduction: Adult rats possess a wide repertoire of 50-kHz ultrasonic vocalizations (USVs), comprising at least a dozen call subtypes. Of these, the trill and flat call subtypes are particularly interesting, as they appear to capture positive or negative affect, respectively. Male rats clearly exhibit inter-individual differences in 50-kHz call rate (i.e., calls/min) and 50-kHz call subtype emission. Less is known about female USV emission, and in particular whether female rats maintain inter-individual differences in 50-kHz call rate and 50-kHz call subtype emission and whether these differences are affected by variations in the estrous cycle.

Methods: To this end, 24 female Long-Evans rats were tested in two Phases, 3-months apart, to examine the longer-term temporal stability of 50-kHz call rate and call subtype emission. Each Phase lasted 10 days and involved daily assessments of estrous cycle stage and USV emission. USVs were measured over a 20-minute period, from rats placed singly in sound-proof boxes.

Conclusions: Our two main measures were 50-kHz call rate and relative prevalence of trill and flat call subtypes. This study aims to provide a foundational understanding of individual differences in 50-kHz vocalizations in female rats and to evaluate the potential contribution of estrous cycle-related variability to these patterns.

53. Intravenous ketamine and immersive virtual reality to treat depression: Study protocol for a pilot randomized clinical trial

Omer A. Syed, MSc ([1],[2]), Lilia Kaustov, PhD ([1],[3]), Connor T.A. Brenna, MD ([1],[3]), Jordan Tarshis, MD ([1],[3]), Ben Safa, MD ([1],[3]), Stephen Choi, MD ([1],[3]), Fahad Alam, MD ([1],[2],[3]), Peter Giacobbe, MD, MSc ([1],[3],[4]). Affiliations: [1]. Sunnybrook Health Sciences Centre, Toronto, ON, Canada [2]. Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada [3]. Department of Anesthesiology and Pain Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada [4]. Department of Psychiatry, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada

Introduction: Ketamine has emerged as a rapid-acting intervention for treatment-resistant depression (TRD), but further attention is required for strategies to sustain the short-lasting therapeutic effects following each treatment session. The unique mechanisms by which ketamine improves mood symptoms are poorly understood, however some research suggests that a dissociative state of consciousness produced by the drug is integral to its antidepressant effect. This state can be emulated using immersive virtual reality (VR), which can also relieve depressive symptoms, suggesting possible mechanistic overlap. However, the combination of VR during ketamine treatments has not been previously studied. In an open-label, proof-of-concept, randomized controlled pilot trial, our primary objective is to determine the feasibility of collecting data for a larger trial examining additive or synergistic effects of ketamine and VR. A secondary objective is to assess whether the combination of ketamine and VR will result in larger and/or more sustained antidepressant effects compared to ketamine alone.

Methods: Twenty-six patients with TRD will be randomized to receive four intravenous ketamine treatments over 2 weeks, either with or without concurrent VR. The VR will immerse participants in a calming nature environment. Feasibility will be measured as the ability to recruit 26 participants and achieve =90% of follow-up completion. VR tolerability will be assessed using Simulator Sickness Questionnaire (SSQ) and adverse events. Depression symptoms will be measured through the clinician-rated Montgomery-Åsberg Depression Rating Scale (MADRS).

Results: The approved study protocol will be presented. Recruitment progress, intervention adherence, and protocol feasibility will be shared.

Conclusion: The combined rapid antidepressant effects of ketamine and the carry-over dissociative effects of VR may improve treatment outcomes compared to ketamine alone. This pilot trial may offer preliminary evidence on the potential for enhancing ketamine's antidepressant effects. Additionally, our results are expected to inform the design of a larger, multi-centre superiority trial.

54. Is There a Prescribing Cascade Linking Pharmacogenetics, Side Effects, and Polypharmacy in Older Adults?

Emytis Tavakoli[1?²?³*], Samar S. M. Elsheikh[³*], Clement C. Zai[³?⁴?⁵], Arun K. Tiwari[³?⁵], Daniel J. Müller[³?⁵?6], James L. Kennedy[³?⁵?7]. Affiliations: [1].Department of Psychiatry, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada [2].The Royal Ottawa Mental Health Centre, Ottawa, ON, Canada [3].Tanenbaum Centre for Pharmacogenetics, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada [4].Department of Psychiatry & Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada [5].Laboratory Medicine and Pathobiology, University of Toronto; Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada 6.Ontario Shores Centre for Mental Health Sciences, Whitby, ON, Canada 7.Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital of Würzburg, Würzburg, Germany

Introduction: Polypharmacy is prevalent among older adults and elevates the risk of side-effect burden. While the pharmacogenetic (PGx) status of an individual can significantly influence their medication metabolism and tolerability, their systemic relationship with polypharmacy, including downstream prescribing cascades, remains poorly defined. This study investigated the direct and indirect associations between PGx metabolizer status, polypharmacy, and medication side

effects, with particular attention to evaluating side-effects as a potential mediator between metabolizer status and polypharmacy outcomes

Methods: We conducted a secondary analysis of baseline data from the Pharmacogenetic Assessment and Clinical Treatment study, including adults =65 years of European ancestry. Selected items from the UKU Side Effect Rating Scale were analyzed. Total polypharmacy was defined as the concurrent use of five or more medications. Regression and causal mediation analyses were performed in R, adjusting for relevant covariates.

Results: The sample included 278 participants (69.6% female). Polypharmacy was significantly associated with increase in nausea/vomiting (ß = 0.31, 95% CI 0.001–0.61, p = 0.049). Lower CYP2C9 activity showed modest associations with increased fatigue (ß = 0.18, 95% CI 0.02–0.33, p = 0.029) and palpitation (ß = 0.14, 95% CI 0.01–0.27, p = 0.031). Higher CYP3A4 activity was associated with reduced hypersomnia (ß = -1.60, 95% CI -2.85 to -0.35, p = 0.013) and nausea/vomiting (ß = -1.40, 95% CI -2.38 to -0.43, p = 0.005). PGx status was not significantly associated with polypharmacy. Furthermore, mediation analyses showed no significant total, direct, or indirect effects of PGx status on polypharmacy through side-effect burden.

Conclusion: Pharmacogenetic status and polypharmacy were each associated with selected side effects in older adults. No evidence of a prescribing cascade was observed, suggesting these associations may reflect parallel pathways. Longitudinal studies are needed to further clarify these relationships.

55. Immune Genetic Architecture of Schizophrenia: Brain Expression Profiles and Clinical Subtype Analysis

Kowsar Teymouri, Sohom Dey, Fernanda Dos Santos, Jennie Pouget, Clement C. Zai, Daniel Felsky, George Foussias, Vanessa Goncalves, James L. Kennedy

Introduction: Schizophrenia (SCZ) is a complex and heterogeneous disorder. The most recent GWAS identified 287 loci associated with SCZ risk. An extensive body of research has demonstrated the significant role of the immune system in the pathophysiology of SCZ; however, the underlying mechanism remains poorly understood. This study investigates the role of immune genes in SCZ by examining their expression profiles and associations with treatment-resistant schizophrenia (TRS), age of onset (AO), Global Assessment of Functioning (GAF) score, and number of hospitalizations (NOH).

Methods: We identified 1227 immune genes across 22 KEGG immune pathways and annotated SNPs to genes using SCZ GWAS summary statistics and MAGMA. Immune-specific genes significantly associated with SCZ (N=77; p < 4.47e-05) were analyzed using FUMA Gene2Func to assess tissue expression profiles. SNPs corresponding to significant immune genes were used to calculate immune-polygenic risk scores (immune-PRS) with PRSice. We used our Toronto Schizophrenia sample (N=188) as the target cohort, comprising patients over 18 years old diagnosed with schizophrenia. Associations between immune-PRS and TRS, AO, GAF, NOH, suicide attempt and suicide ideation were assessed. Sex, age, and five principal components were included as covariates.

Results: We identified 77 immune genes associated with SCZ risk. FUMA analysis demonstrated that a subset of these immune genes were enriched in brain tissues and their

expression was downregulated in three brain regions (e. g. anterior cingulate cortex), linking immune processes to neural substrates in SCZ. Furthermore, immune-PRS was not significantly associated with any of the clinical profiles.

Conclusion: This study is the first to examine schizophrenia subtypes using immune-specific PRS and gene expression profiles. Our results highlight the differential expression profiles of the immune genes in the brain and emphasize the significant role of the immune system in the pathophysiology of SCZ. However, further research using larger datasets is required to validate these results.

56. Cortical Oscillatory Signatures of Innate Fear: Reduced Alpha and Gamma Power during Predator Odour Exposure in Mice

Evan Tigley, BSc; Bosong Wang, MSc; Asim Ahmed, MSc; Jordyn Crawford, BSc; Demi Ma, BSc; Brenda Wan, UR; Nidhi Kotikalapudi, BSc; Kartik Murari, Phd; Ning Cheng, Phd
Neuroscience, University of Calgary, Calgary, Alberta, Canada
Introduction: Alterations in cortical oscillations, particularly alpha and gamma, have been implicated in stress, anxiety, and neuropsychiatric conditions involving dysregulated fear, such as Post-Traumatic Stress Disorder. This study utilized electroencephalography (EEG) to investigate changes in cortical oscillatory activity and freezing behaviour during exposure to predatory odours in mice, with the hypothesis that alpha and gamma power would be altered. c-Fos immunohistochemistry was used to measure neuronal activation in brain regions involved in fear circuits. By integrating cortical oscillations, behaviour, and c-Fos expression, this study characterizes neural activity associated with innate fear.

Methods: Frontal-parietal differential EEG was recorded on female postnatal day 40 FVB wild-type mice during three conditions: homecage (baseline), freezing chamber without urine, and freezing chamber with fox (n=5) or coyote (n=5) urine. Freezing time was analyzed using the EzTrack program. EEG signal parameters included absolute and relative power, peak alpha frequency, and theta-beta ratio. Following testing, c-Fos immunohistochemistry was performed in the medial prefrontal cortex, basolateral amygdala, and medial amygdala (MEA).

Results: Absolute and relative alpha and gamma power significantly decreased from no-urine to urine conditions in both fox ($p < 0.01$) and coyote ($p < 0.01$) urine exposure. c-Fos expression increased in the MEA only ($p < 0.05$). Freezing times did not differ between fox and coyote urine exposure.

Conclusion: These findings demonstrate that innate fear is associated with reductions in alpha and gamma cortical oscillatory activity, which indicates changes in neural synchrony under threatening contexts and aligns with findings from human stress and anxiety studies. No differences in freezing times between fox and coyote urine exposure suggest a conserved response across aversive cues. Elevated MEA c-Fos expression supports its role in olfactory threat processing. As similar cortical oscillatory alterations are reported in anxiety-related disorders, this study may provide a translationally relevant foundation for understanding fear dysregulation.

57. Sex Differences in Pain's Alteration of Endocannabinoid System Gene Expression

Haley A. Vecchiarelli, PhD; Bartosz Lelas, BSc; Ana L. Simal, MSc; Danielle Halasz, MSc; Jaime Tuling, MSc; Giannina Descalzi, PhD Department of Biomedical Sciences, Ontario Veterinary College, University of Guelph, Guelph, ON, Canada

Introduction: Chronic pain is a debilitating condition affecting over 20% of adults in Canada, particularly women. Despite its widespread prevalence and being a major global health concern, current treatments are inadequate. Additionally, chronic pain is a strong risk factor for affective conditions; people experiencing chronic pain show altered brain activity in the anterior cingulate cortex (ACC), nucleus accumbens (NAc) and basolateral amygdala (BLA). People suffering from chronic pain indicate that cannabis may reduce pain symptoms—however, how the endocannabinoid system is altered in pain chronification is not well understood, particularly across sexes.

Methods: Young adult (8-10 weeks old) female and male C57BL/6CR mice were used. Inflammatory pain was modelled using Complete Freund's Adjuvant (CFA) and neuropathic pain was modelled using the spared nerve injury (SNI) model. QPCR was performed for the following endocannabinoid system targets: Crn1, Crn2, Ppara, Grm5, Dagla, Daglb, with Gapdh as a control. Data were compared using a two-tailed t-test between each pain model and its control per sex and time point.

Results: Following CFA, there were limited changes in the ACC, with males having reduced Ppara ($p<0.05$) at 24 hrs, and, in the NAc, females had increased Crn2 ($p<0.05$) at 24 hr—but no other significant changes in other genes examined. In the BLA, however, females had increased Crn1 ($p<0.05$) and Grm5 ($p<0.05$) at 72 hr, whereas males had increased Grm5 ($p<0.001$), Dagla ($p<0.01$) and Daglb ($p<0.05$) at 72 hr. For SNI, in the BLA, females had an increase in Daglb ($p<0.01$) and Ppara ($p<0.05$), whereas males had an increase in Grm5 ($p<0.01$) 5 days post-injury.

Conclusions: These preliminary data suggest that there are early sex differences in the endocannabinoid system with inflammatory and neuropathic pain—which may be related to sex differences in pain chronification. Understanding the mechanisms of chronic pain and co-morbid anxiodepressive symptoms may identify novel therapies.

58. Polygenic Risk for Alzheimer's Disease is Not Associated with Neurocognitive Performance in Youth with or without Bipolar Disorder

Gabrielle Walach, MSc[1,2]; Kody G. Kennedy, PhD[1]; Mikaela K. Dimick, PhD[1]; Clement C. Zai, PhD[1,2]; Benjamin I. Goldstein, MD PhD[1,2,3] [1]Centre for Youth Bipolar Disorder, Centre for Addiction and Mental Health, Toronto, ON, Canada; [2]Department of Pharmacology, University of Toronto, Toronto, ON, Canada; [3]Department of Psychiatry, University of Toronto, Toronto, ON, Canada.

Introduction: Bipolar disorder (BD) is associated with neurocognitive deficits and increased risk for Alzheimer's disease (AD). We examined the association of an AD polygenic risk score (AD-PRS) with sustained attention, working memory, and cognitive flexibility in youth with BD.

Methods: Participants included 128 youth of European ancestry (n=69 BD, n=59 controls), ages 13–20. Sustained attention, visuospatial working memory, and cognitive flexibility were

assessed using the Rapid Visual Processing, Spatial Span, and Intra-Extra Dimensional Set Shift tasks from the Cambridge Neuropsychological Test Automated Battery, including subtest and composite scores. AD-PRS was calculated using PRScs-auto. General linear models examined associations of AD-PRS with neurocognitive measures in the overall sample, stratified by diagnosis and sex, and interaction effects. Covariates included age, sex, diagnosis, IQ, and the first two genetic principal components.

Results: There were no significant findings in the overall sample, diagnostic subgroups, or diagnosis interaction models. In the overall sample, higher AD-PRS was associated with higher Spatial Span composite scores in males (ß=0.29, p=0.04), to a significantly greater extent than females (interaction: ß=-0.18, p=0.03; n.s. after Bonferroni correction).

Conclusion: These findings align with the lack of association of AD genetic risk with neurocognition in community studies in youth. While this is a single study with limited power, results suggest that there are not large effects of AD-PRS on executive function in youth with BD, despite their increased risk of AD. Further research examining neuroimaging correlates of AD polygenic risk may help clarify early-life mechanisms linking polygenic risk to later neurodegenerative vulnerability.

59. Changes in Future-Oriented Decision-Making Following Neuromodulation in Treatment-Resistant MDD and OCD

Micaela Wiseman, MSc[1,2], Rohina Kumar, BSc[1], Tulip Marawi, MSc[1,3], Valery Sit, BSc[1], Anusha Baskaran, PhD[1], R. Shayna Rosenbaum, PhD[4], Julia G. Halilova, PhD[4], Benjamin Davison, MD, PhD[1,2],6, Nir Lipsman, MD, PhD[1,2],6, Sean Nestor, MD, PhD[1,2,5], Peter Giacobbe, MD, PhD[1,2,5], Jennifer S. Rabin, PhD[1,2],6 [1]Harquail Centre for Neuromodulation, Sunnybrook Research Institute, Toronto, ON; [2]Institute of Medical Sciences, University of Toronto, Toronto, ON; [3]Graduate Department of Psychological Clinical Science, University of Toronto Scarborough, Toronto, ON; [4]Department of Psychology, York University, Toronto, ON; [5]Department of Psychiatry, University of Toronto, Toronto, ON; 6Department of Neurosurgery, University of Toronto, Toronto, ON

Introduction: Delay discounting (DD) indexes future-oriented decision-making by quantifying the devaluation of delayed rewards relative to immediate ones. Steeper discounting has been observed in major depressive disorder (MDD) and obsessive-compulsive disorder (OCD) and is associated with greater symptom severity. DD engages frontal-striatal circuits targeted by neuromodulation approaches for MDD and OCD, such as deep brain stimulation (DBS) and focused ultrasound (FUS). This study examined whether changes in DD differ between neuromodulation responders and non-responders, and whether these changes track symptom improvement.

Methods: Thirty patients with treatment-resistant MDD (n=15) or OCD (n=15) undergoing DBS or FUS were assessed at baseline and 12-month follow-up. At each timepoint, participants completed a DD task. Performance was quantified using area under the curve (AUC), with higher values reflecting less discounting and greater future orientation. Treatment response was defined as =50% reduction in HAM-D scores (MDD) and =35% reduction in Y-BOCS scores (OCD). Linear mixed-effects models assessed longitudinal changes in AUC, and regression analyses examined associations between AUC change and symptom improvement, adjusting for age, sex, and years of education.

Results: A significant Diagnosis × Responder × Time interaction showed diagnosis-specific effects (ß = -0.15, p = .015). In MDD, responders showed greater increases in AUC compared to non-responders (ß = 0.15, p = .002), indicating more future-oriented decision-making following treatment. Greater reductions in HAM-D scores were associated with increases in AUC (ß = 0.01, p = .040). In OCD, no significant associations were observed, and changes in Y-BOCS scores were not associated with AUC.

Conclusion: In treatment-resistant MDD, symptom improvement following neuromodulation was accompanied by increased future-oriented decision-making, reflected in reduced delay discounting. This change was not observed in OCD, suggesting differences in how these conditions change with treatment.

60. Role of serotonin receptors in treatment-induced serotonin axon reinnervation in a mouse model of post-stroke depression

Qiya Xu[1,2], Faranak Vahid-Ansari[2], Alberto Francisco Fuentes Alvarenga[1,2], Mireille Daigle[2], Paul R. Albert[2] [1]Neuroscience Graduate Program, Cellular and Molecular Medicine, University of Ottawa, ON, Canada; [2]Ottawa Hospital Research Institute (Neuroscience) and Brain and Mind Research Institute, University of Ottawa, ON, Canada

Background: Post-stroke depression (PSD) affects about one-third of stroke patients. Depression is linked to serotonin (5HT) deficiency and PSD patients are often treated with selective serotonin reuptake inhibitors (SSRIs), which enhance 5HT levels. However, SSRIs also trigger 5HT autoinhibition and require 3-4 weeks to see therapeutic effect, and only 30% of PSD patients remit. Thus, better treatment is required. To model PSD, mice were given stroke by endothelin-1 injection at the left medial prefrontal cortex (mPFC). These mice show anxiety- and depression phenotypes that are reversed by chronic SSRI, which restore 5-HT projections. In this study, we use bilateral optogenetic stimulation in Pet-ChR2 mice to directly release 5HT at the stroke site to achieve a treatment effect. Objectives: To examine whether blocking 5HT receptors can prevent opto-stimulation-induced 5HT axon regrowth, brain activity changes and behavior outcomes.

Methods: Pet-ChR2 mice that express channelrdhodopsin-2 (ChR2) in 5-HT neurons and wildtype (WT) mice and bilateral light fibre implants at the cingulate gyrus (CG) and stroke. After 2-week surgery recovery, all mice had chronic 20-Hz optogenetic stimulation (3x5min/day for 5-days; and 24hr before each behavioral test). Mice receive 5-HT receptor antagonist intraperitoneal injection (WAY100635 and Ketanserin) 15 minutes before each opto-stimulation. We use behaviour tests to assess treatment effect and utilized immunofluorescence staining to assess cellular changes.

Results: Optostimulation of Pet-ChR2 mice restored behavioral phenotypes of stroke mice, and significantly increased of axonal density in the lesion area, comparing with WT mice; however, no recovery was observed in the amygdala and hippocampus. Upon systemic 5-HT antagonist injection, Pet-ChR2 mice no longer show antidepressant and anxiolytic effects.

Conclusion: This study suggests that local activation of 5-HT release at the mPFC can enhance 5HT axonal regrowth and improve behavioral phenotype after stroke, an effect that is mediated by activating 5HT1A and/or 5-HT2A receptors.

61. Associations Between FAAH Binding, Neural Function, and Negative Valence in Cannabis Use Disorder: A Multimodal Imaging Study

Miray Youssef, MSc[1?2]; Maria T. Secara, BSc[1?2]; Claudia Poluga, MSc[1?2]; Shahtaj S. Dheda, BSc[1]; Hassan Abdulrasul, MSc[1?2]; Christina Pereira, BSc[1?2]; Lucas Narciso, PhD[1]; Jerry Warsh, PhD[1?2]; Matthew Sloan, PhD[1?2]; Bernard Le Foll, PhD[1?2]; Stefan Kloiber, PhD[1?2]; Isabelle Boileau, PhD*[1?2]; Peter Zhukovsky, PhD*[1?2] [1]Centre for Addiction and Mental Health, Toronto, Ontario, Canada [2]University of Toronto, Toronto, Ontario, Canada *Equally contributed/co-supervised this work

Introduction: Cannabis use disorder (CUD) is characterized by endocannabinoid system dysregulation and may also be linked to abnormal emotion processing. This study examined endocannabinoid enzyme FAAH binding and negative emotional processing and their associations in CUD compared to healthy controls (HC).

Methods: 16 adults with CUD and 62 HCs completed FAAH [^{11}C]CURB positron emission tomography and the Hariri faces task during fMRI, which probes neural circuits involved in processing negative emotional facial expressions. Group differences in baseline [^{11}C]CURB was assessed across 7 regions of interest. Voxel-wise task fMRI activation was compared between groups using permutation-based cluster inference ($Z>2.8$, $p<0.05$). Linear models were used to examine differences in fMRI activation between CUD vs. HC and assess whether amygdala FAAH binding predicted task-based fMRI activation in CUD and HC. All analyses controlled for age, sex, and body mass index.

Results: Baseline FAAH binding was significantly lower in individuals with CUD relative to HC across multiple brain regions ($p<0.05$). During the Hariri faces task, CUD showed lower activation to angry and fearful faces vs. shapes within the right insula ($p=0.0392$; $Z=3.54$) and anterior cingulate cortex ($p=0.0198$; $Z=3.54$). FAAH-fMRI associations in the amygdala differed significantly by group ($p=0.001$), where higher FAAH binding was associated with lower amygdala activation during the faces task ($R^2adj=0.55$, $p=0.002$) in CUD, and not in HC ($R^2adj=0.05$, $p>0.05$).

Conclusion: Consistent with previous findings, individuals with CUD showed lower baseline FAAH binding across multiple brain regions and blunted insula and anterior cingulate cortex activation to negative emotional faces relative to HC. Greater amygdala activation during the task was also associated with lower amygdala FAAH binding in CUD, suggesting a relationship between endocannabinoid signaling and altered emotional processing.

62. Synaptic Density in Youth with PTSD: Preliminary Findings from the Toronto Adolescent and Youth (TAY) Cohort's PET [18F]SynVesT-1 Sub-Study

Maia Zilberman[1,2], Cassie Cote[1,2], Lujia (Ember) Yu[2], Jennifer Truong[2], Yuliya Nikolova[2], Erin Dickie[2], Stephanie Ameis[1,2], Kimberly Desmond[1,2], Lucas Narciso[1,2], Carme Uribe[1,2], Dafna Kahana[1,2], Neil Vasdev[1,2], Daniel Felsky[1,2], Benjamin Goldstein[1,2], Kristin Cleverley[1,2], Darren Courtney[1,2], Lisa Hawke[1,2], Nicole Kozloff[1,2], Alexia Polillo[2], Martin Rotenberg[1,2], Lena Quilty[1,2], Wei Wang[2], George Foussias[1,2], Aristotle Voineskos[1,2], Jerry Warsh[1,2], M. Omair Husain[1,2] & Isabelle Boileau[1,2] [1]University of Toronto [2]Centre for Addiction and Mental Health

Introduction: Exposure to trauma during childhood can negatively impact neurodevelopmental processes. Findings from rodent studies suggest that early life adversity is associated with lower synaptic density. Here, we used PET imaging of the radiotracer [18F]SynVesT-1, a probe for synaptic vesicle glycoprotein 2A, a marker of presynaptic density, to investigate differences in synaptic density between treatment-seeking youth participating in the TAY Cohort Study with post-traumatic stress disorder (PTSD) compared to healthy controls.

Methods: Participants completed a PET scan with [18F]SynVesT-1. MRI was used to delineate six regions of interest (ROI): prefrontal, anterior cingulate, and temporal cortices, amygdala, hippocampus, and striatum. Time-activity curves were fitted using a simplified reference tissue model with the centrum semiovale as the reference region. Non-displaceable binding potential (BPnd), an index of synaptic density, was estimated for each region and compared between groups. ANOVA was conducted to investigate between-group differences in synaptic density.

Results: Twenty-five participants (7M, 18F, 21.5 years old) met DSM 5 criteria for PTSD and other current co-morbid diagnoses. Thirty-one participants (17M, 14F, 22.3 years old) were age-matched healthy controls. There was no main effect of PTSD on synaptic density ($F(1, 54)=0.009$, $p=0.923$), but a significant group by ROI interaction ($F(3.496, 54)=17.639$, $p<0.001$), such that presynaptic density was lower in the temporal cortex of participants with PTSD (-8%, $p=0.022$).

Conclusion: This is the first study to investigate the relationship between PTSD and synaptic density in youth. We extend the limited adult literature employing PET imaging for presynaptic density in participants with PTSD. These results are subject to limitations, however, as we did not control for co-morbid mental health disorders or medication use.



Looking forward to seeing you in 2027!